RECENT ADVANCES IN UROLOGY

by

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WITH THE ASSISTANCE OF SPECIALIST CONTRIBUTORS

With 83 Illustrations



LONDON
J & A CHURCHILL LTD
104 GLOUCESTER PLACE, W 1
1957

Printed in Great Britain

PREFACE

There are very few surgeons to-day who could honestly claim to feel equally confident when operating inside the skull the thorax and the abdomen This is not due to the fact that surgical techniques are becoming more difficult or more numerous, but rather to the fact that the indications for each operation are becoming more selective while the alternative and the ancillary methods of treatment are becoming more complex

The surgical technique of an operation is generally much easier to master than the indications for its use and it is not the operative surgery which is becoming specialized so much as the study and treatment of the surgical pathology Nowhere is this more true than in urology

It is becoming increasingly difficult to read all of the ever growing volume of urological literature, let alone glance through the general surgical journals as well It is even more difficult to decide from the literature what constitutes a real clinical advance rather than an addition to our scientific knowledge Although most of this scientific knowledge will inevitably lead to further clinical advances in due course, such advances are not a continuous process. There are long periods during which from the patients point of view there are no advances, even though our data on the particular subject may be increasing rapidly

This book deals only with aspects of urology in which new data are accumulating, or in which recent advances have occurred. My colleagues, who have contributed to the work could all be regarded as specialists within a speciality and I am extremely grateful to them for their co-operation. We have attempted to discuss recent advances rather than review recent literature and would apologize for omissions and commissions which may appear obvious to all in a few years time

I wish to express my thanks to the many authors who have allowed me to use their illustrations and blocks while I am particularly grateful to Miss Freda Wadsworth, the medical artist at the Institute of Urology for the outstanding quality of her illustrations

My thanks are also due to Mr E. Stride A I B.P of the P
graphic Department, Hillingdon Hospital, and to Mr I
Bartholomew A I.B P A.R.P S of the Photographic Depart
in the Institute of Urology for the X ray and other photogr
reproductions throughout the text.

It has been a great privilege to work with Messrs. J & A Chu
in this venture.

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CHAPTER 1

MEDICAL PROBLEMS IN UROLOGY

by

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PHYSIOLOGY

In health the volume and composition of the extracellular fluid remains virtually constant largely due to the activity of the kidneys However although the stability of the internal environment depends on renal function the converse is partially true for if there are gross disturbances of the body fluids, from whatever cause then renal function may suffer It is necessary to have some knowledge of the physiology of the kidneys and the body fluids in order to understand and treat renal failure. Only an outline of these extensive subjects can be given here with more emphasis on the important advances than on the well established facts.

Renal Function

The kidney in performing its regulatory function is required to excrete metabolic end products, foreign substances and surplus normal constituents of the body fluids, and in addition to conserve substances such as glucose amino-acids, water and electrolytes which are necessary to the body The urine formed will therefore be at one and the same time, both more and less concentrated than the blood plasma in respect of different solutes.

Knowledge of renal physiology has not changed in broad outline since Marshall showed that tubular excretion occurred and Cushny s theory of filtration and reabsorption was finally modified Since then however many of the details of renal function have become clearer and quantitative measurement of different aspects of function has become possible

It is convenient to consider renal function in three stages renal

blood flow glomerular function and tubular function Before doing so it may be as well to remind the reader of the principle of clearance tests, which figure prominently in researches in renal physiology

If the concentration of any substance in the urine is U mgm./ml. and the rate of urine formation is V ml./min., then $U \times V$ mgm of this substance are excreted per minute

If at the same time, the plasma concentration of this substance is P mgm./ml. then $\frac{U \times V}{P}$ ml of plasma must have been cleared of the substance per minute.

Renal Blood Flow

There is a very large renal blood flow Smith *et al* (1938) showed that, when present in low concentrations in the plasma, the substance diodrast appeared in the urine at such a rate that about 700 ml. of plasma must have been cleared of it per minute. Sodium p-amino-hippurate (PAH) was shown to be cleared at the same rate and these clearance rates were thought to represent the total renal plasma flow Warren *et al* (1944) were able to make simultaneous analyses of arterial and renal vein blood by catheterisation of the renal vein and show that PAH was virtually removed from the blood in one passage through the kidney This confirmed the hypothesis that the PAH clearance is a measure of renal plasma flow

Glomerular Filtration

Although actual analysis of the fluid in the capsular space, as was achieved by Richards (1938) in the kidneys of amphibia, is obviously impossible in man it is universally accepted that at the glomerulus there is a simple physical process of filtration of the plasma through the glomerular capillaries the fluid formed being a protein-free replica of plasma—an ultra filtrate The effective filtration pressure is the blood pressure in the capillaries less the opposing osmotic pressure of the plasma proteins and the pressure within the capsular space. The inulin clearance test developed by Homer Smith and his colleagues (1951) provides a method of measurement of the rate of formation of filtrate, for inulin is filtered at the glomeruli but

neither excreted nor reabsorbed by the tubules In the healthy adult man the rate averages 130 ml /min or over 180 litres a day This test is acknowledged to be valid in health and probably measures the rate of glomerular filtration in the diseased kidney but there is a possibility that inulin might diffuse back to the blood stream through the tubular epithelium when this is severely damaged

Tubular Function

In broad terms the function of the tubules is to modify the glomerular filtrate in such a way that excretion of the urine formed will always defend the composition and volume of the extracellular fluid in spite of the variable metabolic loads which tend continually to alter this. This implies a complexity and flexibility of function in contrast to the simple mechanical process of filtration at the glomerulus. The tubular epithelium performs three tasks it re absorbs some things back to the blood stream excretes others into the urine and in regulating the acid base balance of the body synthesises new substances.

Reabsorption. Clearly most of the huge quantity of filtrate must be reabsorbed and in normal circumstances virtually all the glucose, 99 per cent of the water and sodium and between 40 per cent and 50 per cent of the urea will be returned to the blood stream

The modern view is that the proximal tubule is the site of reabsorption of glucose and most of the other substances that are to be retained. About 80 per cent of the water accompanies these solutes leaving a fluid which is approximately isotonic with blood plasma. This phase has been described by Smith (1951) as obligatory reabsorption "

Mechanisms of Reabsorption. The reabsorption of glucose requires an active transport mechanism calling for the expenditure of energy for it proceeds against concentration gradients Shannon and Fisher (1938) showed that the tubules can only handle a limited quantity of glucose in a given time, and when this is exceeded glycosuria will occur This work has been extended to the reabsorption of other substances and it now appears that the tubular transport of amino-acids phosphate, sulphate and vitamin C exhibits the same phenomenon i e. there is a relatively sharp limit to its

capacity This, the maximal tubular transport capacity measured in mgm./min is often denoted by the symbol Tm. It is of course different for different solutes and whereas the Tm for glucose is such that at normal plasma concentrations and filtration rates all is absorbed and none is excreted, phosphate, having a much lower Tm normally appears in the urine.

Sodium and other major electrolytes are also reabsorbed by active mechanisms limited in scope, but it is not possible to determine a Tm value for them.

Urea in contrast is returned to the blood stream by a process of simple diffusion through the tubular epithelium

The processes so far described are comparatively rigid, and the power of fine adjustment which the kidney must possess appears to reside in the distal tubule. Here the remaining 20 per cent of the filtrate is modified so that either a concentrated or dilute urine is excreted. This implies the existence of mechanisms allowing reabsorption of water and solutes independently of each other

Reabsorption of Water There are two distinct phases involved in water reabsorption As already mentioned about 80 per cent of the water of the glomerular filtrate is reabsorbed in the proximal tubule simply because of the osmotic gradients created by the active reabsorption of solutes such as glucose. This process, controlled entirely by osmotic forces cannot vary to meet the water requirements of the body

In the distal tubule active reabsorption of water can occur independently of solutes and it is in this stage, which Smith (1951) has called the stage of facultative reabsorption, that the necessary adjustments of the rate of water excretion take place. The mechanism is controlled by the antidiuretic hormone of the posterior pituitary and the action of this hormone is to increase the reabsorption of water but not of solutes. As a consequence of this conservation of water a small volume of concentrated urine is formed. Conversely when the secretion of the hormone is inhibited relatively less water than solutes will be reabsorbed and a large volume of dilute urine will be excreted. The stimulus to the secretion of antidiuretic hormone is an increase in tonicity or osmolarity of the extracellular fluid which, in turn, is normally caused by a low ingestion of water

Naturally there is a limit to this process of distal water reabsorption and, even when the body can ill spare water and the urine is of maximal concentration about 600 ml of urine must be formed in excreting a normal daily load of solutes

The regulation of water reabsorption in the distal tubule is not the only factor controlling urine volume and concentration If the glomerular filtrate contains an increased amount of any osmotically active solute which is not reabsorbed by the proximal tubule then the passive osmotic reabsorption of water at this site will be retarded Furthermore, the active reabsorption of other solutes may be diminished, simply because their concentration in the tubular fluid will fall and so increase the osmotic force opposing their reabsorption As a consequence a greatly increased flow of fluid will be delivered to the distal tubule, a flow which overwhelms the reabsorptive mechanisms in this segment. The resultant increased urine flow is termed an osmotic diuresis.

The studies of Raporport *et al* (1949) have shown that when an osmotic diuresis is induced by the administration of various solutes, the rate of urine formation increases as the solute load is increased but at the same time the total concentration or osmolarity of the urine decreases, even in subjects who have been deprived of water However unlike the diuresis induced by drinking a lot of water the osmolarity of the urine can never fall below that of blood plasma.

The important fact which emerges from this concept of osmotic diuresis is that whenever the kidney has to excrete a large load of any solute there will be an abnormal loss of water and perhaps of less importance, an abnormal loss of other solutes such as sodium.

Platt (1952) suggests that in chronic renal disease the polyuria and inability to form a concentrated urine can be explained by osmotic diuresis In chronic renal disease the number of functioning nephrons is reduced and each will therefore have to take a larger share of the total solute load requiring excretion Each nephron will in consequence be working continually under the stress of an osmotic diuresis even though the total load of solutes (urea, sodium etc) which claims excretion from the body is no greater than normal. This theory fits certain observations much better than the classical assumption that the inability to form a concentrated urine is due to

damage to the tubular epithelium. In 1892 Rose Bradford showed that polyuria occurred in dogs when much of the renal parenchyma was removed surgically In these circumstances it is difficult to visualise damage in the tubular epithelium of the surviving nephrons.

Sodium Reabsorption. Sodium conservation is also under hormonal influences, the adrenal cortical hormones—in particular aldosterone—promoting its reabsorption. However other factors influence the renal handling of sodium. When the intake of sodium is low its excretion is diminished and furthermore when there is a sharp reduction in the rate of glomerular filtration then sodium excretion will also fall in both cases because a greater proportion of the filtered sodium is reabsorbed In addition the tubular mechanisms for the excretion of acid products of metabolism allow conservation of sodium which would otherwise be lost.

Tubular Excretion

In 1923 Marshall showed that the tubular epithelium had the ability to transport phenol red from the plasma to the urine so proving the existence of tubular excretion. Later when the glomerular filtration rate could be measured accurately it became evident that other substances were excreted in the urine at faster rates than was possible by filtration alone. Creatinine and potassium are naturally occurring substances excreted by the tubules and many foreign substances, e.g. penicillin, are handled in the same way

Acid-Base Regulation

Normally the acid products of metabolism exceed the basic and these are neutralised in the body-fluids by combination with base, very largely sodium, derived from bicarbonate. If the acids were excreted in combination with sodium then there would be a rapid loss of body sodium The urine pH never drops below about 4 8 which means that the strong acids, such as H_2SO_4 are not excreted as free acids However in the tubule, mechanisms exist which allow excretion of acid without a loss of the fixed bases of the body Essentially these consist of the formation of NH_3 and H^+ ions by the tubule cells. NH_3 was originally thought to be derived from urea, but it is now known to be formed from amino-acids such as

glutamine by enzymatic activity Pitts and Alexander (1945) adduced evidence to show that hydrogen ions are formed in the tubule cells from H_2CO_3 produced from CO_2 and H_2O under the influence of carbonic anhydrase These H^+ ions are exchanged for cations such as sodium which can be reabsorbed. This explains the excretion of NaH_2PO_4 instead of Na_2HPO_4 However the substitution of H^+ for sodium in NaCl would leave HCl which cannot be excreted as such, for it is a strong acid and almost completely dissociated in solution The NH_3 formed in the cells now migrates to the urine in response to the increased hydrogen ion concentration and NH_4Cl is excreted.

THE BODY FLUIDS

A major medical advance has been seen in the improved management of the dehydrated patient resulting from a better understanding of the anatomy and physiology of the body fluids. Only a brief account of this important subject can be given here, and for a fuller description the reader is referred to the 1946 Croonian Lectures delivered by Marriott and the monograph of Gamble (1950)

Anatomy and Physiology

The body fluids exist in two main compartments—intracellular and extracellular and the latter can be further divided into the interstitial fluid and the blood plasma. All these fluids are watery solutions, the intracellular water being about 40 per cent, the interstitial about 12–15 per cent and the plasma water about 5 per cent of the total body weight.

Water moves freely between all compartments and there is also a free interchange between the plasma and the interstitial fluid of all solutes except the plasma proteins The plasma and interstitial fluid will therefore have essentially the same composition

Substances entering into metabolic processes within the cell must be able to enter or leave it Nevertheless, the cell membrane behaves as though it is impermeable to the major electrolytes of the body fluids in that quite different concentrations of these are maintained on either side of it presumably by processes needing energy

expenditure. The composition of the extracellular fluid is therefore quite different from that of the fluid within the cell though, since the cell membrane is permeable to water they will have the same total osmolarity The approximate composition of each is shown below

Extracellular Fluid (E.C.F.)		Intracellular Fluid (I.C.F.)	
Cations	Anions	Cations	Anions
Na 142 mEq./l	Cl 103 mEq./l	K 157 mEq./l	PO 113 mEq./l
K 5 "	HCO_3 27 "	Na 14 "	Protein 74 "
Ca 5 "	SO 1 "	Mg 26 "	HCO_3 10 "
Mg 3 "	HPO_4 2 "		
	Organic acids 6 "		
	Protein 16 "		

Units of Measurement

In reporting on the chemical analysis of body fluids it is obviously advantageous to express the concentration of the various electrolytes in terms of their chemical equivalence to each other rather than by their actual weights. The equivalent weight of a substance is the weight which will combine with or displace one gramme atom of *hydrogen and a milli-equivalent is 1/1000th part of this*

The equivalent weight of monovalent elements such as Na^+ Cl^- K^+ is equal to their atomic weight. In divalent elements such as Ca^{++} or Mg^{++} it will be half the atomic weight and so on.

Thus 23 mgm. of Na or 35 mgm. Cl will each be 1 milli-equivalent. To convert milligrammes per 100 ml. into milli-equivalents per litre, multiply by 10 to give milligrammes per litre, then divide by the atomic weight of the element concerned and finally multiply by the valency i e.

$$\text{mEq/l} = \frac{\text{mgm./100 ml.} \times 10}{\text{Atomic wt.}} \times \text{Valency}$$

The osmotic force exerted by ions will be independent of their valency so that a divalent ion will have the same osmolar value as a monovalent one

The adoption of these units of measurements for body fluid electrolytes is almost universal but as yet the more familiar units of grammes and milligrammes are still commonly used in describing fluids used in replacement therapy a complication which adds to the difficulty of computing how much of a particular intravenous fluid should be given to replace total body deficits

Body Fluid Disturbances

Deficiency of the body fluids i.e. dehydration can be caused by a lack of water of electrolytes or salt and by a combination of both. In practice the combination of water and salt loss is most commonly seen but conditions approximating to isolated water or salt deficiency can exist, and their effects are different. Experimental work on salt depletion by McCance (1936 1938) and the clinical work of Nadal *et al* (1941) have led to a much better understanding of the effects of these different forms of dehydration These effects will be described separately for although the separation may be somewhat artificial from a clinical standpoint, this method of presentation facilitates explanation and understanding of the principles involved

Effects of Water and of Salt Lack

Before either of these is considered, two points need emphasis

The immediate effects of both water and salt lack are borne by the extracellular fluid (E.C.F) but the changes which occur in this rapidly induce alterations in the intracellular fluid (I C F)

At first the kidney attempts to defend the tonicity of the E.C.F at the expense of volume though later this defence fails and changes in tonicity occur

Water Lack. The body can only economise in water to a limited extent and if none is ingested there are inevitable daily losses of about 1 litre from the skin and respiratory tract and 600 ml. in the urine, these being counterbalanced by only 400–500 ml. of water obtained from metabolic processes In water deficiency the initial effect is that the E C F becomes hypertonic. Water therefore passes from the cells into the E.C F to restore osmotic equilibrium and cellular as well as extracellular dehydration will occur

Salt Lack In salt deficiency without fully parallel water lack the initial tendency is for the E.C.F to become hypotonic and the kidney will excrete water though retain salt, in an attempt to preserve tonicity Furthermore, since the E.C.F becomes hypotonic, water will shift into the cells. In consequence only the extracellular fluid volume will suffer

It should be mentioned that although the term salt lack is commonly used it is more exact to speak of sodium lack. The body cannot substitute any other cation for sodium whereas the total sum of anions can be made up by bicarbonate when chloride is lacking. Furthermore, although sodium and chloride are often lost from the body together sodium can be lost with other anions. Of course a disproportionate loss between sodium and chloride will alter the composition of the E.C F and cause an acidosis or alkalosis but the tonicity of the E.C F depends largely on its sodium content.

This scheme of body fluid disturbances is to some extent an over simplification for it ignores changes in intracellular electrolytes. Such changes do occur and will be mentioned briefly in the section on potassium

Ætiology

Water Deficiency Severe acute water lack will occur when there is no access to water or when the patient cannot drink because of coma or severe dysphagia. A lesser degree of water lack is common. It occurs in feeble patients who just cannot make the effort to drink, and, in urological practice, in the prostatic patient who avoids drinking in order to relieve his nocturnal frequency or dysuria. In general, therefore, it is due to lack of ingestion.

Salt Deficiency This occurs in patients who have suffered abnormal electrolyte losses via the alimentary tract, skin or even kidneys, and are treated by the forcing of water by mouth rectal tap-water or 5 per cent dextrose intravenously In fact, they lose both water and salt, but only water is replaced. In contrast to water lack, salt deficiency is due to abnormal losses rather than failure of ingestion

A combination of water and salt lack is much more common than pure deficiency of either A patient who loses water and electrolytes

and cannot drink because of vomiting still suffers inevitable water losses from the skin and renal tract. The vomitus will also be slightly more hypotonic than the E.C.F

Clinical Findings

Water Deficiency The outstanding early symptom is thirst. The tongue and skin are dry Provided renal function is normal the urine will be scanty of high specific gravity and will contain chlorides. As the deficiency progresses the body temperature may rise and mental changes of disorientation mania and finally coma occur Since the I C.F is sharing the water lack with the E.C.F a reduction in plasma volume and signs of circulatory insufficiency are late occurrences

Examination of the blood may show a rise in hæmatocrit and concentration of plasma proteins, and the blood urea and plasma electrolyte concentrations may also rise but all of these are late manifestations.

Salt Deficiency There is an absence of thirst. The tongue is wrinkled but may be moist and the skin is inelastic Until circulatory failure supervenes the urine volume is not decreased indeed if water intake is liberal there may be a diuresis, and chlorides are absent from the urine. Lassitude, apathy muscular weakness and even cramps headache and nausea are common Because the volume of the E.C F is reduced signs of circulatory deficiency occur comparatively soon

The signs range from slight dizziness and postural hypotension in the early stages, to the picture of severe circulatory failure when the deficiency is advanced. By then the diuresis of early stages may have given way to complete anuria

A rise in hæmatocrit, plasma proteins and blood urea will also occur in this condition The concentrations of plasma electrolytes will vary At first they may be normal but later as the defence of tonicity fails they will fall, particularly if water alone has been administered

In patients who have lost both salt and water the clinical findings are more variable. For example, thirst may be absent in water lack

when salt deficiency is also present, and the scanty urine will contain no chlorides

The diagnosis of body fluid disturbances is not difficult if an accurate case history can be obtained particularly if this contains careful observations on the amounts and type of fluid that the patient has lost and what has already been given in replacement. There is a tendency to neglect these observations in favour of immediate plasma electrolyte determinations These are, of course, invaluable in the complicated or advanced case when they may reveal markedly disproportionate losses between anions and cations or unsuspected changes in plasma potassium levels. However it must be remembered that normal plasma electrolyte concentrations are compatible with considerable degrees of combined water and salt lack.

Treatment

In planning replacement of body fluid losses it is necessary to consider the composition of the fluids to be given, the amounts which are needed and the route of administration

Composition of Replacement Fluids. Patients who are suffering from uncomplicated water lack need water only If they cannot drink it may be given rectally by stomach tube or intravenously as 5 per cent dextrose. Isotonic saline or other electrolyte solutions must *not* be given to these patients some of the water of such solutions would be lost from the skin and respiratory tract leaving the kidneys the task of excreting the electrolytes in what remains of the water Kidneys already embarrassed by water lack may not be able to do this and consequently the E.C.F will become even more hypertonic.

Equally patients with salt or sodium deficiency need salt not water Water alone will only increase the hypotonicity of the E.C.F and will then either be excreted in the urine or if renal failure has occurred because of circulatory insufficiency shift into the cells and cause dangerous water intoxication Isotonic saline suffices for the majority of patients with sodium deficiency Admittedly the ratio of sodium to chloride (1 1) in isotonic saline is not quite the same as in the E C.F (1·4 1) and may differ greatly from the ratio of these

two ions in fluids lost from the body particularly in losses from the alimentary canal However the kidney by selective excretion of one or the other ion will repair the ionic structure of the E.C F There are exceptions to this general rule When there are gross but roughly equivalent deficits of sodium and chloride e.g. in a patient with severe sweating who has only had water in replacement then for roughly every 4 volumes of isotonic saline 1 volume of 1/6 molar sodium lactate should be given Similarly when there has been a much greater loss of sodium than chloride with a resultant acidosis, again some of the sodium should be replaced as 1/6 molar lactate In addition isotonic saline does not replace the potassium deficit which will arise when there are long continued gastro-intestinal losses.

When there is a combination of water and salt lack as is common isotonic saline or other isotonic electrolyte solutions will not provide enough water in proportion to electrolytes. Extra water must be given and if it is necessary to use the intravenous route it must be given as 5 per cent dextrose in water

The Amount of Fluid Needed. As well as replacing pre-existing deficits this must also cover continuing abnormal and normal losses. The most difficult problem is to estimate the initial deficiency In general clinical findings are a more useful guide than laboratory investigations. The history is usually only helpful in this quantitative sense when there have been acute and recent abnormal body fluid losses. It must also be remembered that considerable deficits are necessary before many of the clinical signs mentioned appear for example in an adult man lassitude and postural hypotension may be the only signs of an E.C F deficit of about 3 litres and signs of definite circulatory failure indicate losses of 5 litres or more. Changes in volume of the E.C.F occur sooner than changes in tonicity and for that reason laboratory evidence of hæmoconcentration i e. a rise in hæmoglobin hæmatocrit plasma protein or specific gravity may be found before there is any appreciable change in plasma electrolytes Similarly the blood urea will often be raised before the plasma electrolytes change If however the plasma sodium concentration is diminished, then a rough estimate of the total deficit can be made by the use of various formulæ Black (1953)

suggests that the number of litres of isotonic saline can be computed from the formula $\frac{140 - Na \times 40}{140}$ where Na is the plasma concentration of sodium. He emphasises that this only provides a very rough guide.

In spite of the limited help which can be obtained from these laboratory investigations they should not be omitted for they will provide a base-line from which to judge progress during therapy

Simple observations on the urine can however be very helpful. If the urine is scanty and its specific gravity reasonably high then a water deficit is present.

If chloride is absent from the urine then a salt deficit exists. Marriott (1947) stresses the simplicity and importance of performing the quick method of estimating urinary chlorides described by Fantus (1936) In the majority of cases this a very helpful procedure, but it must be remembered that there may be chloride in the urine even though a deficit of sodium is present. This may be the case when there are abnormal renal losses of salt as in Addison s disease.

Abnormal losses which continue after the patient comes under medical supervision should, of course, be measured it is then easy to replace them by equivalent amounts Finally the inevitable daily water losses must be covered This requirement is provided by 1 litre plus the volume of water lost in the urine. Since the aim should be to obtain a urine volume of at least 1 5 litres per day the daily water requirement is about 2 5 litres.

Taking into account all these requirements it will be realised that the severe case may need a very large volume of replacement fluid consideration must therefore be given to the speed of administration. As a general rule in these severe cases, about 50 per cent of the estimated deficit should be repaired in the first 12 hours.

The Route of Administration. The advantages and disadvantages of the various routes that can be used are well known and only a few opinions are offered. Fluids should be given orally whenever this is possible. If parenteral routes are necessary the advantages of the intravenous infusion probably outweigh its dangers and disadvantages. It should always be used for dextrose solutions and whenever large volumes have to be given Furthermore, the patient

suffers less immobilisation and discomfort from an intravenous drip into a forearm vein than from intramuscular or subcutaneous injections.

Special Problems in Urological Cases. The urologist is mainly concerned with body fluid disturbances arising from abnormal renal losses.

The kidney attempts to defend the composition of the E.C.F by the excretion of water and conservation of sodium in salt deficiency and by the conservation of water and excretion of concentrated urine in water deficiency The damaged kidney unable to form a concentrated urine, cannot economise in water and still excrete a normal solute load. Similarly for various reasons—impairment of the normal mechanisms for excreting acid products, impaired tubular reabsorptive capacity for sodium or because surviving nephrons may be working under the stress of an osmotic diuresis—the damaged kidney may not be able to conserve sodium The dangerous effects of water and salt lack will therefore ensue more rapidly in patients with renal insufficiency

Even when there is no appreciable intrinsic functional renal damage, the patient with a raised blood urea from obstruction to the lower urinary tract will need to expend more water than normal in eliminating accumulated nitrogenous waste products when obstruction is relieved Recognition of these factors has led to the widely adopted expedient of maintaining a high fluid intake in such cases

The dangers of sodium lack are not perhaps so well appreciated Certainly the normal kidney economises in sodium better than water and, even in renal insufficiency severe and rapid urinary sodium losses are rare. Wilson *et al* (1951) described patients who following the relief of lower urinary tract obstruction temporarily suffered enormous urinary sodium losses such an occurrence again appears to be uncommon and must not be confused with the excretion of excess sodium and water which may have accumulated in the body during a period of urinary retention Nevertheless, either because of temporary or permanent renal disability some urological patients will lose more sodium than normal Such losses will be less evident than those from the alimentary canal and will therefore evade early recognition.

Potassium

Potassium is the chief cation of the I C F., and much the greater portion of body potassium is intracellular However the small amount which is present in the E.C.F is important for its concentration cannot vary greatly either way without causing disturbances of myocardial and voluntary muscle contraction I C.F cannot be analysed directly in life, and it is largely due to the work of Darrow (1945 1946) who used indirect methods of analysis, that we now know that depletion of intracellular potassium may occur in various conditions.

Because the amount of potassium entering the E.C F balances the amount leaving it, the concentration normally varies very little. The E.C.F will gain potassium from the food or by transfer from the cells it will lose it in the urine, from the alimentary tract or because potassium is transferred into the cells. The E.C.F concentration is not an index of the state of total body potassium, though usually a low plasma potassium (hypokalæmia) reflects low intracellular levels. However a normal or high plasma potassium (hyperkalæmia) can exist with a total body deficit for in tissue break down or cellular dehydration, potassium will shift into the E.C.F and, if renal excretion does not keep pace with this, the plasma concentration will rise. This will only occur when the rate of entry into the E.C F is rapid or the renal excretion of potassium is impaired normally the kidneys will promptly excrete this additional potassium load. In contrast, the kidneys do not conserve potassium efficiently and, even when there is no intake, urinary losses continue, though as shown by Black and Milne (1952) these losses gradually diminish

Finally it should be noted that although the effects of adrenocortical hormones on total body potassium are complex, they all have the effect of increasing the renal excretion of this substance.

Ætiology of Potassium Disturbances

Hyperkalæmia may be due to renal failure but only when this is severe or of rapid onset. It occurs particularly in oliguric or anuric renal failure. It may be present in Addison s disease, particularly during a crisis. Finally potassium intoxication may be due to a

rapid or excessive intravenous administration of potassium salts

The causes of potassium deficiency are more numerous in general it occurs whenever losses in the urine or from the alimentary tract exceed the intake.

Following surgical operation there is invariably an increased excretion of potassium in the urine This phenomenon which has been fully discussed by Moore and Ball (1952) is thought to be due to release of adrenocortical hormones and must be distinguished from the loss of potassium along with nitrogen and other tissue components, which occurs simply because of cellular breakdown It is maximal on the day of operation only lasts for 2 or 3 days and, in the majority of patients, is of no clinical significance being quickly repaired by dietary intake. However this loss which will be an addition to normal urinary losses, may contribute to clinically significant potassium deficiency in patients who are maintained for several days on potassium-free intravenous fluids. Eliel *et al* (1950) have reported a series of such cases

Potassium deficiency may result from vomiting and diarrhoea for the alimentary secretions, particularly gastric juice, contain potassium.

Excessive loss due to renal disease is uncommon but may occur in the rather rare specific tubular diseases of childhood the Fanconi syndrome and renal tubular acidosis. Even more rarely there are cases of chronic renal failure in adults in which loss of potassium in the urine is the outstanding feature of the illness.

Various forms of acidosis including that which may follow uretero-colic transplantation can lead to potassium deficiency It frequently becomes apparent during the early stage of recovery from diabetic acidosis

Overdosage with adrenocortical hormones, particularly DOCA and natural overactivity of the adrenal cortex in Cushing s syndrome and primary aldosteronism (Conn 1955) are other causes.

In practice it occurs most commonly when there have been abnormal losses from the alimentary tract, or from chronic intra cellular dehydration, which have been replaced solely by potassium free fluids. Indeed the intravenous infusion of solutions of sodium salts may accentuate urinary potassium losses.

Finally it must be noted that an alkalosis is often associated w potassium deficiency an alkalosis which may not be corrected u potassium is given Possibly this is due to the migration of N and H+ ions into the cells in place of the K+ ions which are lost fr them as suggested by Cooke *et al* (1952) To complicate matt a primary alkalosis e.g. caused by an excess ingestion of alkalies, lead to a potassium deficiency Whichever comes first, the prese of one should lead to awareness of the possible presence of the oth

Clinical Features

Potassium intoxication can be rapidly fatal. The early sympt of muscular weakness with diminished tendon reflexes progres quickly to frank paralysis Respirations may be shallow a laboured due to involvement of respiratory muscles. Numbness the extremities is often present and the pulse may be slow a irregular Death results from disturbances in myocardial conducti and contraction There are two diagnostic aids determination the plasma potassium and the electrocardiogram which sho characteristic changes. Since changes in both may precede obvi clinical signs they should be carried out preferably daily in circu stances where potassium intoxication can arise.

In potassium deficiency lethargy apathy anorexia and naus abdominal distension and muscular weakness are common symptor The abdominal distension may progress to a frank paralytic ile and the muscular weakness to a stage not far short of paraly The plasma potassium level is usually low and there are ag characteristic changes in the electrocardiogram.

It should be noted that there is no precise correlation between t degree of hyper and hypokalæmia and the clinical manifestatic of potassium intoxication and deficiency particularly in the case the latter It is accepted that the effects of potassium intoxicati are due to a rise in extracellular potassium concentration It is n so certain that a lowered extracellular concentration is the cause all the manifestations of potassium deficiency One practical poi must be remembered When blood is taken for potassiu determinations it must be sent to the laboratory immediately It necessary to separate the plasma, or serum from the cells as so

as possible for otherwise some potassium will diffuse from the erythrocytes into the plasma and so falsify the readings.

Treatment

The treatment of potassium intoxication will be mentioned in the treatment of acute renal failure

Potassium Deficiency Because of the dangers of potassium intoxication certain precautions are necessary in replacement therapy The oral route is much the safest and it is generally unwise to administer more than 100 mEq., i.e. approximately 4 G., of potassium in 24 hours. Various salts can be given by mouth e.g. the chloride, citrate, acetate or bicarbonate. 2 G of potassium chloride will provide roughly 1 G of potassium and this can be given 6- or 8-hourly in fruit drinks

When intravenous therapy is necessary even greater care must be taken. It is generally agreed that the concentration of potassium in solutions for intravenous use must not exceed 40 mEq./l that no more than 1 litre of such a solution must be given in 3 hours and again, that no more than 100 mEq of potassium must be given in 24 hours. Many solutions suitable for intravenous use have been described these contain anything from 10 to 40 mEq of potassium per litre Perhaps the best known is Darrow's "K-lactate" solution which contains approximately 36 mEq of potassium per litre Le Quesne (1954) has described two simple solutions each of which contains 3 0 G of potassium chloride i.e. 40 mEq of potassium per litre.

Potassium loss is commonly associated with sodium and water deficiency which may have led to oliguria and temporary impairment of renal function This will increase the risk of inducing potassium intoxication. In these circumstances it is best to correct some of the sodium and water loss and see that the urinary output is rising before giving potassium intravenously

RENAL FAILURE

Classification

Renal failure may be due to diminution of renal blood flow lesions of the kidney itself or obstruction to the outflow of urine that is, to pre-renal renal or post renal causes.

Other classifications are in use. Firstly all parts of the nephron may not be affected equally in disease, and in consequence there may be a relatively selective impairment of glomerular filtration or of various tubular activities. Glomerular failure will be characterised by failure of excretion Urea clearance will be low the blood urea will rapidly rise, but any urine formed will be of high specific gravity This is seen in the early stages of acute nephritis, and in renal failure due to pre-renal causes Impairment of tubular function is characterised by failure of conservation. Inability to conserve water and, to a lesser extent, electrolytes reflects an inadequate ability to modify the glomerular filtrate. There are diseases, such as renal glycosuria and cystinuria, in which only one specific function of the tubules is impaired, although the manifestations of these disorders would not commonly be regarded as renal failure.

Secondly as Rosenheim (1951) has pointed out, renal failure may be reversible or irreversible. Recovery can be expected when failure is due to pre and post renal causes, and when it is due to certain acute lesions of the kidney itself However when renal failure is due to chronic renal disease, that is when scar tissue has replaced much of the parenchyma, it is irreversible.

In practice the position is often more complicated. To give an example in a patient with lower urinary tract obstruction there may be loss of renal parenchyma because of hydro-nephrosis or scarring from previous pyelo-nephritis. He may at the same time be suffering from an acute pyelo-nephritis and the renal blood flow may be diminished because of severe dehydration from vomiting. In this case pre- and post renal factors, as well as reversible and irreversible renal factors, are all contributing to the state of renal failure.

Pre-renal Uræmia

This term is commonly applied to renal failure due to pre-renal causes whether or not a state of uræmia is present. Strictly speaking the word uræmia should be reserved for the symptom-complex which results from renal failure with retention of nitrogenous waste products. Since these clinical manifestations are not always present, many authorities prefer the term pre renal azotæmia azotæmia merely denoting that there is a raised blood non protein nitrogen.

Ætiology It is generally accepted that pre-renal azotæmia is due to a failure of glomerular filtration because of deficient blood flow through the glomeruli. Clinical and experimental observations support this concept. Azotæmia occurs in traumatic shock, hæmorrhage, severe body fluid losses from vomiting, diarrhœa etc., and also in the acute heart failure which may follow myocardial infarction. The common factor in all these conditions is circulatory failure. It used to be thought that changes in the composition of the E.C.F., e.g. a deficiency of chloride, were important in the causation of this type of azotæmia. Nowadays more importance is attached to reduction in its volume: this may of course be consequent on loss of electrolytes, especially sodium. It must be admitted that azotæmia may occur in alkalosis from over-ingestion of alkalies, when there is no obvious extracellular dehydration, and the ætiology of this sort of azotæmia is not fully understood.

In the experimental field many investigators have utilised the techniques of inulin clearance, to measure glomerular filtration rate, and diodrast or PAH clearance to measure renal plasma flow, in patients suffering from conditions that can lead to pre-renal azotæmia. McCance and Widdowson (1939) showed that the inulin clearance was reduced in diabetic coma. Black *et al.* (1941) showed reduction in inulin and Perabrodil clearances in patients with gastro-intestinal hæmorrhage. Lauson *et al.* (1944) showed a reduction in glomerular filtration and renal blood flow in cases of traumatic shock and, moreover, found that the renal blood flow was disproportionately decreased when correlated with measurements of blood pressure and cardiac output, findings suggesting that renal vasoconstriction had occurred.

It is easy to understand that a failure of glomerular filtration can occur when the systemic blood pressure is very low, for then the effective filtration pressure in the glomerulus will drop. However, it is important to remember that the blood pressure may be maintained in the face of a diminished circulatory volume by vasoconstriction in organs whose activity is not immediately vital to survival, and it is now generally held that such vasoconstriction does occur in the kidney. This offers an explanation of failure of glomerular function in cases where there has been no obvious sustained hypotension, a

failure probably mediated by constriction of the afferent glomerular arteriole.

Finally post mortem examination in cases of pre-renal azotæmia fails to reveal any lesions in the kidney adequate to account for the azotæmia.

Other factors may contribute to the rise in blood urea, such as an accelerated endogenous protein breakdown from trauma or infection, or absorption of nitrogen from altered blood in gastro-intestinal hæmorrhage.

Clinical Features. These are often dominated by the signs and symptoms of the underlying disease, but signs of uræmia such as muscular twitching, progressive mental and physical weakness, pruritus nausea and vomiting may occur The blood urea may rise rapidly but other chemical changes in the plasma are inconstant, for they depend on the underlying disease. For example, when there has been a loss of E.C.F from vomiting then chloride may be reduced, and so to a lesser extent sodium and an alkalosis may be present. However in pre renal uræmia following the acute circulatory failure of myocardial infarction the chemistry may be normal except for the raised urea.

There is an oliguria, and any urine formed will have a fairly high specific gravity findings which are to be expected in this purely functional form of glomerular failure

Treatment. This consists essentially in the treatment of shock or hæmorrhage, or in replacement of body fluid losses, as the case may be In addition any infections should be vigorously treated and further tissue trauma avoided.

Failure due to Acute Renal Lesions

Acute renal failure may be due to diseases such as acute glomerulotubular nephritis, acute pyelo-nephritis or polyarteritis nodosa. Such conditions will not be considered here. However the group of diseases which Fishberg (1954) has named the necrotising nephroses " will be described, for they have been the subject of many recent communications

The Necrotising Nephroses

Although the occurrence of acute fatal uræmia following black water fever and crushing injuries has been on clinical record for many years the observations of Bywaters and Beall (1941) on renal failure following crushing injuries to the limbs initiated the modern extensive researches into the subject

The condition is characterised clinically by the rapid development of severe oliguria or even anuria and morphologically by lesions which are confined to the renal tubules This fairly well defined renal disorder may follow a variety of causes such as intravascular hæmolysis, severe shock and hæmorrhage gross depletion of water and electrolytes and exposure to nephrotoxic substances. It has been given many names related in some instances to ætiological features, e.g. *shock kidney* *transfusion kidney* *hæmoglobinuric nephrosis* and in others to the morphological lesion e.g. acute nephrosis lower nephron nephrosis or necrotising nephrosis." The term renal shut-down " is also used

Pathology

In fatal cases, from whatever cause, the lesions are predominantly tubular They consist of areas of degeneration necrosis and actual rupture of the basement membrane leading to loss of continuity of the tubular walls Oliver (1951) using the technique of individual nephron dissection has made an outstanding contribution to the understanding of the pathology and by showing that the focal disruptive or tubulorhexic lesions might occur in any part of the tubule has made the term lower nephron nephrosis unacceptable.

The pathogenesis of these lesions has been the subject of many recent studies which have been reviewed by Waugh (1953) Various factors, toxic or allergic, may operate in individual cases depending on the *causative disease state but current medical opinion would* seem to accord renal ischæmia the predominant role in the pathogenesis.

Pathogenesis of Symptoms

The cause of the severe oliguria which is characteristic has been the subject of a great deal of research in the past decade Studies

such as that of Bull *et al* (1950) seem to show that a marked decrease in renal blood flow and glomerular filtration rate are concerned in the production of oliguria In certain types of necrotising nephrosis, e.g. experimental uranium poisoning in animals, there is fairly clear evidence of increased and unselective back-diffusion of filtrate through the damaged tubules While this factor is not proved with certainty in human cases it may operate. Another possibility and *one which would explain the fairly rapid return of urine flow in* recovering patients is that interstitial œdema is the cause of the oliguria. In other cases there may be mechanical blockage of the lumen of the tubules by casts and debris.

The oliguric phase is succeeded in surviving patients by return of urine flow which may progress rapidly to a marked diuresis. In earlier reports it was emphasised that in this stage an uncontrolled loss of water and electrolytes was to be expected, this being ascribed to the inability of the recovering tubule cells to perform osmotic work and respond to normal hormonal influences. While there is undoubtedly a lack of the normal functional flexibility of the renal tubule, Swan and Merrill (1953) suggest that this water and salt loss may be due initially to an accumulation during the oliguric phase, and that the polyuria is subsequently maintained by the generally adopted line of treatment of attempting to replace daily losses *in toto* thus defeating any regulatory function which the kidney is attempting

Clinical Features and Diagnosis

The salient early feature is severe oliguria which persists even if a diminished circulatory volume is restored It is noteworthy that the oliguric phase in this condition is often described as a period of anuria Swan and Merrill (1953) in their comprehensive analysis of the clinical features, point out that complete anuria is rare, and is more commonly seen in other conditions of acute renal shut-down e.g. obstructive anuria or severe acute nephritis This point may therefore on occasion help to differentiate cases which need active intervention from those that require conservative management. It also emphasises the importance of really accurate measurements of urinary output

The specific gravity of the urine becomes fixed at about 1010 and the urine contains protein and depending on the cause of the illness may contain blood pigments

The blood pressure may be low at first because of shock or hæmorrhage, but characteristically tends to be moderately elevated after two or three days The blood urea may rise extremely rapidly as may the plasma potassium and uræmic symptoms and the signs of potassium intoxication may ensue

In surviving patients a diuretic phase follows the oliguria but there is often a lag in the fall of blood urea which may even continue to rise for a day or so

It will be realised that there is no hard and fast dividing line between some cases of pre renal azotæmia and some cases of necrotising nephrosis, for the former condition if untreated may progress to the latter Therefore it may be difficult on first seeing the patient to decide whether structural damage has already occurred or whether the oliguria is merely due to a pre renal cause which will respond promptly to replacement therapy The decision will rest mainly on obtaining a good history of fluid losses and their replacement and whether there are clinical signs of dehydration In addition some help may be obtained from estimation of the specific gravity of any urine passed which is usually high in uncomplicated functional renal failure

Treatment of Acute Renal Failure

In the past attempts were made to provoke an early return or urine flow Splanchnic block renal decapsulation and forcing fluids to create a diuresis were some of the methods used to achieve this The first two measures designed to improve renal circulation of reduce intra-renal tension are sound in theory but rarely work in practice possibly by the time they are done renal damage has already occurred Studies such as those of Lattimer (1945) revealed that forcing fluids, when the renal excretion of water is negligible or absent, leads to deaths from cerebral or pulmonary œdema

Recovery of renal function will occur naturally in the majority of patients provided they survive long enough for the processes of recovery to take place This is fundamental to the understanding

of present-day forms of treatment, which are designed solely to prolong survival. There are two ways of achieving this. Firstly to establish a regime which will minimise the effects resulting from a virtual absence of renal excretion—the conservative method of treatment. Secondly to provide some artificial means of eliminating urea and other waste products Conservative management will be described first because it provides the basis of treatment whether or not other methods are necessary

Conservative Management

The Oliguric Phase. Once obstructive anuria or pre renal azotæmia have been excluded, conservative treatment should be instituted. During the phase of severe oliguria the renal excretion of water minerals and the products of protein catabolism are quantitatively negligible. *Thus reduction of protein catabolism and the restriction of water intake to balance extra renal losses are logical steps to take and form the basis of the modern conservative regime.*

The studies of Borst (1948) and the experimental work of Masson *et al* (1950) show that protein catabolism can be minimised by providing an adequate calorie diet derived solely from carbohydrate and fat. Bull *et al* (1949) devised a regime based on these lines. Through a plastic stomach tube, 1 litre of the following mixture was administered every 24 hours

Glucose	400 G
Peanut oil	100 G
Acacia to emulsify	
Water	ad 1 litre

No electrolytes were given but mineral balance was maintained by filtering and readministering any vomit. The principles of management in the oliguric phase have altered little in the past seven years, and this regime is still used with success. However studies such as those of Moore (1952) Swan and Merrill (1953) have indicated that a rapid catabolism of body fat and liberation of water of oxidation may occur in these patients. For this reason the modern tendency is to dispense with most, if not all of the fat and restrict water intake even further Furthermore gastro-intestinal complications such as severe vomiting, ileus, and diarrhœa may make this alimentary

feeding impossible. Merrill (1953) advocates the administration of 50 per cent glucose intravenously To prevent thrombosis this is administered by a plastic catheter placed in an arm or saphenous vein, and threaded so that the tip lies high in the brachial or cephalic vein if the arm is used and the iliac or even vena cava when a leg vein is used This worker also points out that in gauging the amount of fluid to be administered only about 400 ml per day is needed over and above the endogenous water production to balance extra renal losses. Of course additional amounts will be needed to balance any renal or gastro-intestinal loss He believes that a small daily weight loss of 0 3-0·4 kgm provides a good indication of correct fluid balance, but estimation of this requires the provision of accurate bed weighing-scales.

Opinion is still divided as to whether it is necessary to administer electrolytes in order to maintain normal plasma concentrations. As a general rule, provided there are no initial deficits of electrolytes and no abnormal losses from or into the alimentary canal then it is unnecessary and indeed may be dangerous to administer sodium and chloride even though the plasma concentrations tend as is usual, to drop

Retention of potassium must however be promptly corrected Serial electrocardiograms may be a better index to the development of this complication than simple reliance on plasma potassium determinations Merrill (1955) gives a comprehensive survey of the ✓ methods of treatment of this complication These include short term emergency measures, such as the intravenous administration of glucose and insulin which tends to cause transfer of potassium into the cells the infusion of sodium bicarbonate, sodium lactate or calcium gluconate which are physiological antagonists to potassium and the oral or rectal administration of cation exchange resins in the sodium, hydrogen or ammonium phase Persistence or recurrence of this complication may however call for methods of artificial elimination

No hard or fast rule can be given with regard to blood transfusion. Quite apart from any blood loss which may have occurred in the initial illness, there is a tendency for progressive anæmia to occur during this type of renal failure A balance has to be struck between

the dangers of anaemia on the one hand and of circulatory over loading on the other

The Diuretic Phase. Reference has already been made to work suggesting that the widely held concept that this stage is one of uncontrolled water and electrolyte loss may not be strictly true. The implication of this is that any rule of thumb method of attempting the replacement of water and electrolytes in quantities equal to the previous day's losses is likely to lead to a prolongation of the diuretic phase. On the other hand, abnormal losses which need replacement may occur and these can only be gauged from assessment of several factors such as the state of hydration, plasma electrolyte levels and, above all perhaps, the clinical wellbeing of the patient.

Complications. Conservative treatment has reduced the mortality of this disease in the early stages, but it must be emphasised that deaths from infection or from late complications such as pulmonary embolism can and do occur Bull (1953) found infections to be the commonest cause of death in his series of cases. In connection with treatment of infections it should be remembered that excretion of antibiotics will be reduced so that smaller or less frequent doses will be needed, particularly of the more toxic drugs In the prevention of late complications mobilisation of the patient is of prime importance.

The Artificial Kidney and Other Methods of Dialysis

The Artificial Kidney The working principle of the artificial kidney is that of dialysis of blood across a membrane which is permeable to water and crystalloids but not to colloids. If blood is separated by such a membrane from a surrounding bath containing a solution of crystalloids, then any crystalloid, e.g urea, will leave the blood and enter the bath if its concentration in the blood is higher than in the bath The transfer of water will depend on the relative total concentrations of the two solutions, the more concentrated solution gaining water

Attempts to dialyse blood outside the body and then return it are not new In 1913 Abel Turner and Rowntree successfully dialysed urea from a dog's blood by passing it from artery to vein through a cellodin tube immersed in salt solution

Kolff (1947) devised the first clinically successful artificial kidney In his apparatus arterial blood was led through cellophane tubing wound spirally on a rotating drum immersed in a bath of rinsing fluid The blood was returned to a vein by means of a pump Many modifications of this basic design have since been described but essentially they all work in the same way that is by dialysis through cellophane. Clearly such an apparatus can only be used inter mittently for periods of a few hours and its main use therefore is in the treatment of acute potentially reversible types of renal failure

Difficulties and dangers of its use include clotting in the apparatus and conversely hæmorrhage because of the anticoagulants which must be administered Pyrogen reactions hæmolysis and excessive removal or addition of water and electrolytes because of faulty composition of the bath fluid, have also been described Merrill *et al* (1950) claim that many of the hazards have been reduced by modifications to the apparatus and improved technique These include the extensive use of plastic tubing and anti wetting agents to reduce the tendency to clotting modifications to the rotating couplings and the pump which are said to reduce turbulence and therefore hæmolysis due to mechanical trauma to red cells modi fications which facilitate sterilisation with consequent reduction of pyrogen reactions

Other Methods of Dialysis. Putnam (1922) showed in animal experiments that the peritoneum can be made to act as a dialysing membrane. Many workers have described the application of this principle in cases of renal failure, irrigating the peritoneum with large volumes of hypertonic fluid Originally peritoneal lavage was continued for several days but although appreciable quantities of urea could be removed by this means peritonitis was a frequent complication More recently techniques of short-term or inter mittent irrigation have been described using plastic catheters inserted through a trocar Grollman *et al* (1951) using only one catheter introduces irrigating fluid leaves it for 2 hours and then removes it through the same tube continuing this process for as long as 48 hours. Dérot (1949) advocates a different technique introducing a polythene catheter into each flank and maintaining a continuous flow of irrigating fluids but only for periods lasting 12 to 16 hours.

Technically these methods are simpler than the use of the artificial kidney and require no special apparatus. Again, however the *composition of the irrigating fluid has to be carefully assessed*, so that there will be no unwanted removal or addition of electrolytes. Furthermore, there is a risk of introducing peritoneal infection.

The success of the conservative regime has undoubtedly reduced the need for more active measures, such as the use of the artificial kidney Merrill (1955) points out, however that the artificial kidney must be regarded as an adjunct rather than an alternative to conservative treatment. In certain cases, where infection or trauma cause such a rapid catabolic response that conservative treatment cannot control the retention of metabolites, the artificial kidney may be a necessity and even in cases who would probably survive with conservative management alone it may shorten the stage of severe illness and thereby reduce the incidence of late complications

The artificial kidney appears to offer the most efficient method of dialysis, though it is the most complicated. Some of the dangers of this method have already been described, but in the hands of really skilled and experienced teams it appears that these dangers can be minimised. Clearly the nature of the apparatus and the experience that is necessary to use it properly must restrict its use to a few special centres. If this treatment is available, it would appear to have a definite place in the treatment of selected cases.

Failure due to Chronic Renal Lesions

Factors in the Production of Chronic Renal Failure

It is obvious that nothing can restore renal tissue which has been damaged beyond repair When progressive renal failure is due *entirely to destruction of renal parenchyma, as in chronic pye*lonephritis, hydronephrosis, polycystic kidneys and chronic nephritis treatment can only be palliative. Although in urological practice it is common enough to see patients with uræmia which is due entirely to *irreversible renal disease, nevertheless in many cases other* reversible factors will be contributing to the uræmic state These may be pre renal renal and, most commonly post renal.

Pre renal factors are, paradoxically often due to renal"

uræmia, for the vomiting or diarrhœa of chronic renal disease will cause water and electrolyte loss which will in turn increase the renal failure

The occurrence of acute pyelonephritis superimposed upon chronically damaged kidneys provides an example of a potentially reversible renal factor Post renal factors that is obstructive lesions of the urinary tract need not be considered further in this chapter Much more rarely disorders of calcium metabolism may cause renal failure, for this can occur when there is a high serum calcium from hyperparathyroidism vitamin D intoxication or the prolonged ingestion of large quantities of milk and alkalies. The first in particular may cause confusion when uræmia is thought to be due to calculus disease alone. Correction of these metabolic disorders can result in considerable, though often not complete restoration of renal function

Clinical Features

The kidneys like many other organs have a considerable reserve of function and a great deal of the renal parenchyma must be destroyed before renal failure supervenes In addition hypertrophy of surviving nephrons occurs in many chronic diseases of the renal parenchyma.

Three stages of renal functional impairment can be recognised In the first stage the kidney can still preserve a normal composition of the body fluids and functional impairment is only revealed by the performance of renal function tests, such as the urea clearance test or concentration and dilution tests. Although the power of the kidney to perform efficiently under abnormal circumstances is reduced sufficient reserve is usually present to withstand the stresses of surgery In the second stage the kidney is still able to excrete a normal load of waste products but only because the blood urea is raised and at the expense of a greater obligatory water excretion than normal To give a hypothetical example a man with a normal filtration rate of 120 ml /minute and a blood urea of 20 mgm./100 ml will excrete by glomerular filtration 24 mgm of urea per minute and a patient with a blood urea of 80 mgm /100 ml and a glomerular filtration rate of 30 ml /minute will also excrete 24 mgm urea per

minute When the excretion of urea (ignoring for the purpose of this example any back-diffusion through the tubules) is expressed as the volume of blood "cleared" of urea per minute, it can be seen that in the latter patient the function is only 25 per cent of the former Such a stage of chronic, compensated renal failure is of course compatible with many years of life, the prognosis depending on the rate at which further structural and functional damage progresses. In this stage additional loads on renal excretion will result in further nitrogenous retention but if these loads are only temporary they may be withstood, with eventual return to the original state. In *the third stage the kidneys can no longer excrete the daily load of* solutes and the symptoms of uræmia which accompany the progressive retention of urinary constituents supervene.

It is unnecessary to describe all the many symptoms of uræmia. It should be remembered that many of these, e.g skin and gastrointestinal hæmorrhages muscular twitching and true uræmic convulsions, pericarditis, acidotic and Cheyne-Stokes breathing, ulceration of the mouth and fœtid breath, are very late or terminal manifestations when they are due to chronic renal failure. On the other hand, a normochromic anæmia, lassitude and loss of weight may antedate other symptoms by months or even years when renal failure is slowly progressive, as in polycystic disease. Furthermore, there is no correlation between uræmic symptoms and the height of the blood urea, for this may be very high in slowly progressive renal disease without the patient displaying uræmic symptoms. In general the more rapidly renal disease progresses, the more likely are symptoms to be present at any given blood urea level Finally it should be remembered that many of the symptoms which were formerly ascribed to uræmia, e.g transient hemiplegia, blindness and epileptiform convulsions, are now known to be due to the hypertension which so often accompanies all forms of chronic renal disease.

In general medical practice chronic renal failure may evade diagnosis because its early symptoms are relatively non-specific. In urological practice the problem is somewhat different. The question is usually one of appraisal of the degree of renal failure, with particular reference to the fitness of the patient for operation and

as a corollary deciding how much of the impairment of function is due to irreversible renal lesions and how much to reversible factors which will respond to treatment Many of the special renal function tests, particularly clearance tests which depend so much on the accurate measurement of timed urine specimens are impracticable in the presence of lower urinary tract obstruction but in other cases may be of considerable value in pre-operative assessment Excretion urography is, of course, of inestimable value but the other test which is so commonly performed viz. estimation of the blood urea while of value in estimating the degree of renal functional impairment does not indicate how much of this is due solely to renal causes In many cases it is only after correction of pre or post renal factors has been accomplished that assessment of renal function can be made.

Treatment of Chronic Renal Failure

There has been no spectacular advance in the treatment of chronic renal failure. However the more widespread application of physiological principles, better management of body fluid disturbances, the development of chemotherapy and antibiotic treatment and improved laboratory facilities and techniques have all contributed to better management of the patient

The first step in the treatment of chronic renal failure is to deal with any reversible factors which may be present

The damaged kidney can perform neither excretion nor conservation with normal efficiency and it is therefore logical in treatment to adopt measures which will reduce the load of nitrogenous waste products requiring excretion and which will replace abnormal losses of water and electrolytes Before describing dietetic methods which will minimise protein catabolism, it must be mentioned that surgical operation and any type of infection will increase the rate of tissue breakdown

Dietary Treatment Mention has already been made of the reduction in protein catabolism which follows a provision of adequate calories derived solely from carbohydrate and fat. Some protein however must be given to the patient with chronic renal failure and ideally this should be just enough to balance endogenous protein breakdown. Kolff (1952) believes that as little as 20 G of protein

per diem suffices, whereas other authorities would allow more—40 to 50 G However all agree that an adequate calorie intake should be maintained but it is often difficult to achieve this especially in more severe cases when anorexia and nausea may be present. Sometimes a supplement of proprietary carbohydrate and vegetable-oil emulsions, which provide 4 to 5 calories to the millilitre, may be tolerated in 30 to 50 ml. doses by the patient who can manage relatively small meals but often these prove nauseating and it may be necessary initially to utilise intravenous feeding, as described under acute renal failure, or intragastric drips.

Replacement of Abnormal Losses. Some of the causes of abnormal sodium loss in renal failure have already been given and, in addition, abnormal losses from the alimentary canal are frequent in uræmia. *Moreover low sodium diets are often prescribed for the hypertension* which may accompany chronic renal disease. In general a distinction has to be made between patients whose symptoms are due to hyper tension heart failure or œdema and who therefore require sodium restriction and those who have the polyuria and extracellular dehydration of renal failure and may therefore require more sodium. *Gross loss of sodium in the urine can very rarely be the outstanding* feature of chronic renal failure. This condition— salt losing nephritis —first described by Thorn *et al* (1944)—is seen in patients with chronic pyelonephritis, but may occur in other types of chronic renal disease.

Water Requirements

Impairment of the power to form a concentrated urine is an invariable feature of chronic renal failure This means that more water must be expended in the excretion of the daily load of waste products than when renal function is normal It follows therefore that the patient with chronic renal failure has a higher water requirement and should drink more than a normal person. Opinions differ as to the optimum water intake. One school of thought argues that since the specific gravity of the urine is fixed, a greater excretion of solutes can only be obtained by increasing the urine volume. This is true up to a point, but there is usually some capacity to excrete water and solutes independently left to all but the most severely

damaged kidneys and once an optimum urine volume is achie
any further increase will result in negligible increments in sc
excretion Furthermore damaged kidneys may not be abl
excrete excess water as quickly as normal so that forcing fluids
result in hæmodilution as well as causing nausea and anorexia E
case must be decided on its own merits but provided that there
no abnormal extra renal water losses there is usually little to
gained from intakes exceeding 3 to 4 litres a day

Correction of Other Chemical Abnormalities of the F C F

Acidosis, with a decreased plasma alkali reserve is common
when due to breakdown of the tubular mechanisms for excretio
acid products will be accompanied by loss of base In these circ
stances sodium bicarbonate by mouth or when necessary intraven
1/6 molar sodium lactate, will be beneficial If there is phosp
retention with consequent depression of ionised calcium
correction of an acidosis may precipitate tetany It must
remembered that the acidosis of renal failure may be due to reten
of acid metabolites rather than to loss of base and, in these circ
stances, reduction in plasma bicarbonate is a compensa
mechanism to defend the plasma pH These points shoulc
considered before recourse to the massive sodium lactate or bicarl
ate infusions which have been advised in uræmia.

Freeman and Freeman (1941) showed that aluminium hydro
gels will reduce the absorption of phsophorus from the gut, and
oral administration of 20 to 30 ml of these gels three to four ti
a day may help to prevent the raised plasma phosphorus, w
occurs in severe renal failure. Unfortunately their use may p
nauseating and constipating

Symptomatic Treatment. The nausea and vomiting which ca
a distressing feature of uræmia and impede any dietetic treatn
can sometimes be relieved by chlorpromazine in doses of 10 t
mgm orally or 20 to 30 mgm. intramuscularly two or three t
a day This drug may also help to allay the pruritus of uræmi

Renal Homotransplantation

Corneal tissue may be grafted from one individual to another
survive permanently as functioning tissue. There is some evid

that parathyroid grafts may not only take but also survive and work However in general, homografts i e. grafts from one individual to another of the same species, do not survive permanently as such Their value in surgery is to provide a scaffolding for the processes of inflammation and repair Sooner or later the homograft dies and its death is due to an incompatibility between it and the host. There is strong evidence, from studies such as those of Medawar (1944 1946 and 1948) that the host develops generalised antibodies against the tissues of the graft Dempster (1953) has shown in his studies of experimental renal homotransplantation in animals that the transplanted kidney also appears to develop a reaction against the host.

The idea of treating chronic renal failure by providing a new kidney is an attractive theoretical possibility and it presents no insuperable obstacles in surgical technique However as yet, the solution of the problem of biological incompatibility is not in sight.

Hume *et al* (1955) have described a series of cases of human renal homotransplantation In some of these patients the transplanted kidney worked, and worked well enough to prolong survival. However in all cases this success was only temporary and eventually the transplanted kidney ceased to function

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CHAPTER 2

THE CHEMOTHERAPY OF URINARY INFECTIONS

by

K F ANDERSON

CERTAIN fundamental principles of chemotherapy have become accepted since the early days of sulphonamide therapy Infections of the urinary tract however present a more complex problem and it is not always easy or even possible, to give treatment under optimum conditions. An extensive survey of this problem has been carried out by Garrod, Shooter and Curwen (1954) Cases fall into three groups each seeming to carry a different prognosis and some requiring a careful choice of chemotherapeutic drug. The first group of cases, without abnormality of the urinary tract and without history of urinary infection carries a good prognosis. A cure as judged by the elimination of the organism from the urine both at once and at the follow up 2–4 months later can usually be anticipated with any suitable agent indicated by sensitivity testing. The second group of cases includes all those with a previous history of infection and here the prognosis may be only moderately favourable. In the last group where there is definite abnormality of the urinary tract the outlook is frankly poor particularly when surgery cannot be undertaken

The problem is essentially one of choosing a chemotherapeutic substance which is relatively non toxic, which will not increase the damage to an already pathological kidney and which will act efficiently in the face of impaired renal function. Even if these criteria are satisfied the problem set by the emergence of resistant strains is a serious one, and too often the original organism may be eliminated only to be replaced by another In Garrod s series this occurred in 46 per cent of cases whose urine was not sterilised by treatment.

Careful laboratory control cannot be too strongly advocated, since not only will this indicate the most efficient antibacterial substance, but it will also detect the emergence of resistant variants and give some indication as to the completeness of cure. There is undoubtedly a clear relationship between the *in vitro* sensitivity of the infecting organism and the outcome of treatment. The unsatisfactory results which at first occurred with sulphonamide testing have now been eliminated by the use of testing media free from sulphonamide inhibitors, thus bringing the *in vitro* results into line with the clinical findings.

Since, in the majority of cases, the uncomplicated urinary infection will respond to a number of chemotherapeutic substances indicated by laboratory testing, the advances in this field must be directed towards the control of chronic cases and the problems set by resistance and toxicity

Sulphonamides

Recent research has concentrated on producing compounds of diminished toxicity capable of giving high urinary concentrations, without the risk of crystalluria. Sulphafurazole (3 4-dimethyl 5-sulphanilamide-isoxazole) is highly soluble in the physiologically important range of pH 6·0–7 5 (Fig. 1) Svec, Rhoads and Rohr (1946) have studied the solubility absorption and excretion of this compound and have found that its solubility in urine rapidly increases from 60 mgm. per 100 ml. at pH 5·4 to 327 mgm. per 100 ml. at pH 6 14 compared with only 12·9 mgm. per 100 ml. for sulphadiazine at pH 6·4 Approximately 70 per cent of the drug is excreted in the free active form, the remainder being acetylated and inactive. It is of interest that unlike sulphanilamide, which is evenly distributed in the tissues sulphafurazole is almost entirely confined to the extracellular fluids. This indicates that high blood levels may be achieved with relatively small doses and that failure to penetrate the cells may render the drug less toxic (Marshall, 1948) In a clinical trial Stewart and Lash (1950) considered the effectiveness of the compound from the point of view firstly of its ability to sterilise the urine, and secondly of the presence or absence of relapse after cessation of treatment. Only those cases with sterile urine after a

month following the cessation of treatment were regarded as cured The compound appeared effective in controlling infections with *E. coli* Gram positive cocci and some strains of *Ps pyocyanea* and *Proteus* Dosage for an infection of moderate severity is 2 G stat. followed by 1 G every 4-6 hours Therapy should be continued

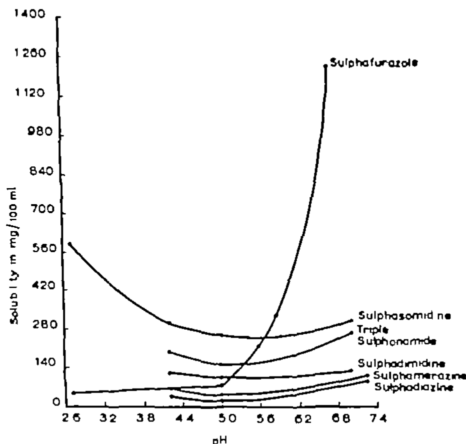
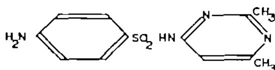


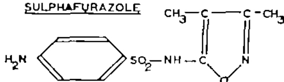
FIG 1 Comparison of the solubility of free sulphonamides in acid urine. (Ziegler *et al.*, 1954)

until the temperature has been normal for at least three days and until urine cultures have been sterile for at least three consecutive occasions.

Sulphamethiazole (2-sulphanilamideo-5-methyl 1 thio 3 4 dia

zole) is a compound structurally similar to sulphafurazole (Fig. 2) It is remarkably non toxic and only between 5 and 10 per cent becomes acetylated Administration of 0 1 G five times daily usually results in urine concentrations of approximately 20 mgm per 100 ml Contrary to the usual practice with sulphonamide drugs, there is no necessity to increase the fluid intake. Indeed,





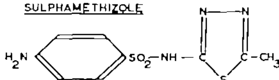


FIG 2. Chemical formula of sulphasomidine (Elkosin) sulphafurazole (Gantrisin), and sulphamethizole (Urolucosil).

restriction may be actually desirable to maintain adequate drug levels in the urine. Warren (1954) treated fourteen cases of *E. coli* infection of the urinary tract with this substance and obtained a complete cure in ten cases There was no evidence of toxicity over long periods of treatment.

Sulphasomidine (6- (p-aminobenzenesulphamideo)-2 4 dimethyl pyrimidine) is another extremely active compound which remains

in the free active form in blood and urine to the extent of some 90 per cent of the total dosage. When used alone, it does not require adjuvant alkali therapy to guard against crystalluria. Daily doses of 5 G. produce average blood levels of 6–10 mgm. A single oral dose of 0·05 G./kgm. will produce a urine concentration of approximately 200 mgm. per 100 ml. in 6 hours. About 86 per cent of the total dose is excreted in 24 hours. Toxic reactions are rare.

Triple sulphonamide mixtures were originally introduced to diminish the risk of crystalluria by reducing the concentration of any one agent whilst maintaining an overall therapeutic level of combined substances. Weinstein and Murphy (1952) find it unwise to use sulphonamides in combination without first determining the *in vitro* sensitivity of the infecting organisms. The antibacterial activity of the various mixtures tends to be completely unpredictable and depression or antagonism of the activity of the components leads to the conclusion that such mixtures are often not as effective as the single agents of which they are composed.

A new sulphonamide, as yet without an approved name is 3-sulphanilamido-6-methoxypyridazine. It has shown interesting properties in the experimental animal which it is hoped will be repeated in man. It has a high solubility in urine and good absorption from the gastro-intestinal tract. Owing to slow urinary excretion it is anticipated that single daily doses may be adequate for most infections, although clinical data is at the moment limited. The N^4-acetyl derivative, which in urine accounts for approximately 30 per cent of the original drug, is relatively insoluble. It is evident that at low flow and with acid urine, it is possible to produce renal crystalluria on therapeutic dosage. The results of further clinical trials are awaited.

Nitrofurantoin

This substance is one of a series of substituted furan derivatives with marked antibacterial activity. Following oral administration it appears in significant concentration in the urine although blood levels at any one time remain extremely low. In consequence, it has been used almost exclusively for infections of the genito-urinary tract. It possesses the unusual property of appearing in the urine

in a state of stable supersaturation If large amounts of nitrofurantoin are dissolved in urine at the blood and glomerular pH of 7 5 reduction of the pH to 5 5 does not produce precipitation The clinical findings of Mintzer *et al* (1953) support the conclusion that crystalluria is unlikely to occur with therapeutic dosage. Nitrofurantoin has a broad spectrum of antibacterial activity and is particularly effective against *E coli* and pathogenic cocci (Richards *et al* 1955) *Pseudomonas infections are not controlled* and although *Proteus* is temporarily inhibited, relapses are frequent during treatment or shortly after cessation. Mintzer *et al.* describe *in vitro* synergism between nitrofurantoin and penicillin and streptomycin, and this may be borne in mind when drug-resistant variants ultimately emerge. The *in vitro* studies of Waisbren and Crowley (1955) indicate that the action of nitrofurantoin is essentially bactericidal Resistance, when it occurs, appears to arise through the action of some drug-inhibiting substance produced by the organism.

On a dosage of 7–10 mgm./kgm./day toxic reactions are few the commonest being nausea and vomiting. This can usually be controlled by ensuring that the drug is taken with, or shortly after food There is no evidence that blood dyscrasias occur on therapeutic doses and examination of the fæces has shown that the flora *of the large bowel remains unaltered*

" Broad-spectrum " Antibiotics

The choice of antibiotic for the control of urinary infections which have passed into the chronic stage will at first be limited by the overall toxicity of the agent. While many of the broad-spectrum antibiotics are extremely effective in eliminating acute uncomplicated infections, there is little doubt that many have toxic properties which make their long-term use a matter for careful clinical judgment. Of these, nausea, vomiting and diarrhœa can be sufficiently severe to warrant discontinuing treatment. Alterations in the micro-flora of the gut, moniliasis and staphylococcal enterocolitis are among the more serious sequelæ of prolonged administration. Even if toxicity does not cut short a course of treatment, the rapidity with which *resistant variants may emerge* can curtail the period over which these substances may be usefully employed (Herrold, 1951)

Oxytetracycline has been subject to a number of clinical trials Nesbitt and co-workers (1951) selected twenty four cases of long standing, with a previous history of treatment with antibiotics or sulphonamides. In two-thirds of the cases, *Ps pyocyanea* or *B aerogenes* was present. Using high oral doses to evaluate toxicity the authors found that six out of their twenty four cases could be rated as good results. Although twenty improved rapidly ten relapsed when the drug was withdrawn and four were re-infected with a new organism. Trafton and Lind (1953) in a further series of thirty five cases, found the percentage of bacteriological as well as clinical cures high. In this series, oxytetracycline was found mainly ineffective against *Proteus* and certain strains of *Staph pyogenes*

Tetracycline has also been investigated in urinary infections by Gohar Makawi and Manoufi (1954) In doses of 500 mgm orally every 6 hours for periods ranging from two courses of 5 days each to 1 week, the urine cleared rapidly in a few days, but remissions were frequent.

Combined Antibiotic Therapy for the Suppression of Resistant Variants

Stern and Elek (1955) have performed important *in vitro* experiments to investigate the use of combinations of two antibiotics as a means of suppressing the emergence of resistant variants of *E coli* Using a gradient plate technique, forty-two strains of coliform bacilli were tested against a number of antibiotics singly and in combination. The authors found that combinations of antibiotics were effective in suppressing the emergence of resistant variants provided that the organisms were sensitive to both antibiotics in the combinations. The chances of a doubly resistant variant arising are so small as to encourage further clinical trials of this method. Attention is drawn by these workers to the importance of bactericidal action in the elimination of urinary infections. Organisms lying dormant under the influence of a purely bacteriostatic substance may cause relapse when therapy is withdrawn The bactericidal action of streptomycin is largely offset by the rapidity with which resistant strains emerge during treatment. However Stern and Elek find that when combined with tetracycline or chloramphenicol streptomycin

retains its bactericidal action whilst resistant variants are suppressed These combinations are found to be the most effective. Such findings have far reaching clinical implications and the techniques can clearly be applied in an effort to eliminate infections with other organisms in addition to those caused by *E. coli* and *B aerogenes*

The Control of Pseudomonas Infections

Infections with various species of *Pseudomonas* are amongst the most intractable encountered in urological practice. Notoriously resistant to most antibiotics and chemotherapeutic agents, it rapidly colonises the genito-urinary tract if combinations of tissue necrosis, stasis and obstruction exist. Owing to its simple nutritional requirements, interference with the enzyme systems of the organism is difficult, and this may in part, account for the failure of most antibacterial agents Although resistance is recognised as a characteristic of the genus *Pseudomonas* it cannot be too strongly emphasised that each strain should be individually tested against all available antibacterial substances. It is impossible to predict the sensitivity spectrum of any one strain, and not infrequently an organism may prove to be sensitive to one of the commoner antibiotics.

If more conventional treatment fails, the use of polymyxin B sulphate offers a reasonable chance of eliminating the infection. This substance is a basic polypeptide derived from *Bacillus polymyxa* The molecule is large and does not penetrate cells nor reach non-vascular areas such as the interior of the eye or the subarachnoid space Intramuscular injection of 20 000 to 40 000 units per kgm body weight results in serum levels of 10–80 units per ml. (Polaski *et al.*, 1949) Most susceptible organisms are destroyed by concentrations of 0 5–20 units of polymyxin B per ml. The antibiotic is bactericidal in action and appears to be absorbed on to the bacterial cell membrane, the permeability of which is altered. In this respect, polymyxin resembles certain cationic detergents. Only very small amounts of the antibiotic appear in the urine after intramuscular administration but favourable results may be expected in acute pyelonephritis presumably due to high serum levels. In infections of the lower urinary tract, polym ay also be administered locally by irrigation using a solu units per ml

The usual therapeutic dosage of 25 000 units/kgm /day produces little evidence of renal irritation although the earlier polymyxins showed marked nephrotoxicity Doses exceeding that quoted may cause proteinuria and even nitrogen retention Where kidney damage already exists, a lower dose should be exhibited with repeated urine examinations to assess the renal condition Polymyxin should certainly not be withheld from *Pyocyaneus* infections of the urinary tract since failure to eliminate the organism can only result in further curtailment of renal function The position of polymyxin B in the treatment of such infections has been fully evaluated by Jawetz (1952) This antibiotic remains the most valuable agent available for the control of these intractable conditions which otherwise carry an extremely poor prognosis.

The Chemotherapy of Genito-urinary Tuberculosis

The introduction of isonicotinic acid hydrazide (INAH) has revolutionised the pre-operative management of genito-urinary tuberculosis. The use of this substance has been fully investigated by Ross Gow and Hill (1951) by Ross (1953) and by Gow (1953) After the early clinical trials of INAH in pulmonary disease, (Joiner *et al* 1952) it became clear that this chemotherapeutic substance could not be used alone since the danger of producing resistant strains of *M tuberculosis* was much greater than when INAH was combined with another antituberculous substance The mechanism by which INAH inhibits the tubercle bacillus is still uncertain but the various enzyme pathways which may be involved have been comprehensively reviewed by Meadow (1956) Combined therapy has become accepted as part of the treatment of both pulmonary and genito-urinary tuberculosis. Various treatment regimens have been designed to reduce the emergence of resistant variants. Streptomycin and INAH can be alternated with one of the thiosemicarbazones and calcium benzamido-salicylate. The two combinations are given for 14 days and are alternated for at least 6 months.

The value of PAS in preventing or delaying the emergence of INAH and streptomycin-resistant variants has been fully confirmed (M R.C. Investigations 1953 1955) Many of the symptoms of intolerance which occur when PAS itself is administered can be

avoided by the use of calcium benzamido-salicylate. This compo undergoes hydrolysis after oral administration to yield PAS A sin dose of 15 G gives an average maximum plasma level of 20 μgm PAS per ml. *With repeated doses of 5 G at 8-hourly interv* steady plasma levels of approximately 18 μgm. of PAS per ml maintained. Urine concentrations are approximately twenty-i times the plasma PAS levels. The drug is well tolerated even at maximum dosage of 21 G per day Combinations of chen therapeutic substances undoubtedly offer the best therapy for control of tuberculosis of the genito-urinary tract and for the prepa tion of those patients suitable for surgery

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CHAPTER 3

RADIOLOGY OF GENITO-URINARY TRACT

RECENT advances in radiology of the genito-urinary tract have included the use of improved types of opaque media new methods of applying such media and the application of the X ray image amplifier to urological work

Opaque Media

Diodone solutions can be injected intramuscularly or even subcutaneously without producing severe reactions in most cases, so that their safety for use in routine excretion urography make them more popular than iodoxyl solutions. Much work has been done to try and increase the radiological density of the medium excreted into the calyces 35 per cent, 50 per cent and 75 per cent solutions have all been urged but it is doubtful if there is enough difference to warrant the use of the stronger solutions which are also more locally irritating and toxic. The strength of the solution injected can have little effect on the strength of the medium finally excreted down the renal tubules. What is more important is the radiological density of the molecules themselves, and recent work has been directed towards increasing the atoms of iodine in the molecules of the injection medium. This has produced several new substances (sodium acetrizoate sodium diacetamido triiodobenzoate, etc.) which contain three instead of two atoms of iodine in the molecule. There is now ample evidence to show that these substances are less toxic than diodone or iodoxyl (Cave, Burfield and Rankin, 1953) while most workers also consider that they do in actual fact produce better radiological definition (Robbins 1951 Byrne and Melick, 1953) In the author's personal experience these new substances are excreted more rapidly so that good calycine definition is often obtained within three minutes of injection while, in general, they appear to cause much less pain in the shoulder and arm and less generalised flushing.

It is important to realise that a patient exhibiting a sensitivity to one contrast medium may not do so to another but this can only be found out by experience, since it is doubtful whether any of the known methods of testing for sensitivity can predict a serious, or even a fatal result (Mullen and Hughes, 1952)

For retrograde pyelography the older sodium iodide solutions have been replaced by dilute solutions of diodone or iodoxyl which, though more expensive, are not irritating to the mucosa, and are much less liable to produce iodism

On occasions when a more viscous solution is required such as during urethrography visciosol or any other water soluble proprietary substance is much more satisfactory than the oily preparations, which give false filling defects due to bubbles of non-opaque urine.

Abdominal Compression

Abdominal compression when properly applied will prevent the too rapid escape of contrast medium from the ureters, and although some exaggerated dilatation of the calycine systems will occur the resultant increased radiological opacity can be of great value, provided the surgeon fully realises what he is looking for While the routine use of compression may give the radiologist a very good film to report upon, it may tell the urologist nothing new at all, since it may be important to know that the calyces are irritable and excrete the medium rapidly or that there is mild ureteric atonia as shown by slow ureteric emptying. This information is not forthcoming unless the surgeon knows exactly what has been done before each film is exposed. Each film has to be examined carefully before the next move is decided upon and unless the whole procedure can be supervised by a radiologist or the surgeon himself it is perhaps better to dispense with compression as a routine measure, but to reserve it for cases where anatomy as opposed to physiology is under investigation. For example, properly applied compression will produce such good calycine detail in tuberculous cases that repeated retrograde examinations can often be avoided, but the technique of the examination requires very careful supervision (Ericsson and Lindblom 1950)

Abdominal Aortography

In 1929 Dos Santos introduced the translumbar method of injecting opaque medium into the abdominal aorta in order to secure radiographs of the arterial tree. He was most enthusiastic about the value of the procedure, but it never became popular In 1936 an adverse report was published by Henline and Moore, who experienced

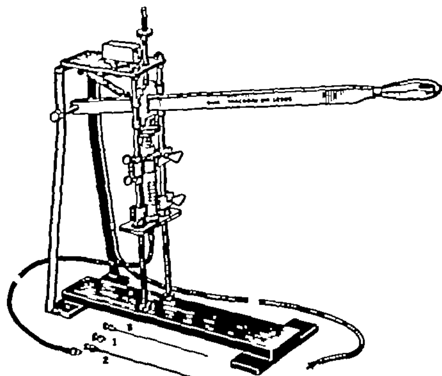


FIG 3 Barr Stirling Injector With this apparatus it is possible to inject 18–20 ml. of opaque medium into the aorta within a second.

several deaths in their dog experiments, and the whole subject was again forgotten until 1942 when both Nelson and Doss in America reported two large series of cases independently In this country credit must go to Griffiths (1950) for reviving interest in the use of aortography in urology and his emphasis of the fact that many thousands of cases had then been reported without fatalities

Technique

The aorta is easily punctured by an 18 S W G needle of at least 15 cm. length which is introduced along the left side of the body of the first lumbar vertebra, as in performing a paravertebral block. Care must be taken to make sure the needle is completely inside the aortic lumen by aspirating blood and injecting normal saline, after which 20–40 ml of diodone solution are injected as rapidly as

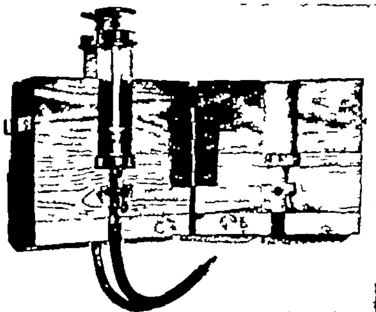


Fig 4 (a)

Fig 4 Authors home-made apparatus for protecting the hands and syringe during rapid injection.

possible Films are then exposed at two-second intervals, commencing just before the end of the injection

In practice, the timing of the exposures presents more difficulty than the puncture of the aorta. However even when the needle has been correctly adjusted a few millimetres of movement may displace it with resultant escape of diodone outside the aorta. This produces an alarming looking radiograph but appears to have no other ill effect. The speed of injection of the medium is an important factor

in securing good contrast so much so that Stirling (1955) has devised a lever apparatus (Fig 3) which applies considerable pressure to the syringe plunger For the ordinary user a home made apparatus such as that depicted in Fig 4 will afford considerable pressure and protect the operator s hands at the same time

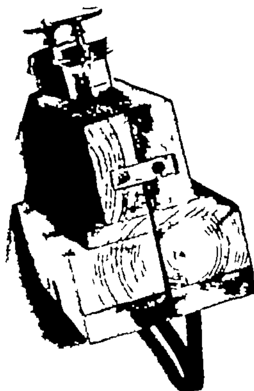


Fig 4 (b)

Interpretation of the films requires some experience, and several phases should be noted. Films during the first few seconds show the aorta, the renal arteries, and their major branches and perhaps the cœliac axis vessels. Two or three seconds later the medium has passed on into the collecting tubules so that the whole renal substance (if it possesses normal tubules) stands out as an opaque

mass—the renogram This picture can be most informative, helping to differentiate between solid and cystic areas and by drawing attention to the abnormal shape of the renal mass. Films taken after a minute or so begin to show the usual excretion pyelogram outlines. The above technique requires a well-trained team and is much easier to carry out with the patient under a general anæsthetic. There is always a certain " hit and miss element about the site of aortic puncture in relation to the cœliac axis and renal arteries with perhaps loss of much of the medium into the splenic and mesenteric vessels.

Femoral Aortography

A more recent development of renal arteriography has been the percutaneous introduction of a plastic catheter into the aorta via the femoral artery This can be performed under local anæsthesia without exposing the femoral vessel and has many advantages over

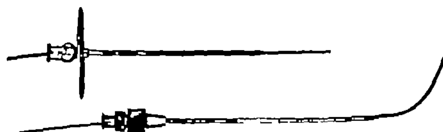


Fig 5 Seldinger needle, stilette and flexible metal leader

the direct needle puncture of the aorta. For example any desired level of the aorta can be selected for the site of release of the opaque medium. The risks of extravasation around the aorta are removed while, more important still the catheter can be left *in situ* without risk of displacement and the patient can be moved frequently into any desired position for radiography

Peirce and Ramsay (Peirce 1951 Peirce and Ramsey 1953) use a method whereby the fine polyethylene catheter is passed down the lumen of a special stop-cock needle combination which has previously been inserted into the femoral artery by direct percutaneous puncture. This method requires a rather thick needle in order to pass a catheter

large enough to inject an adequate amount of medium in a short time. Seldinger (1953) has overcome this problem by the use of an ingenious apparatus which allows of the replacement of the needle by a catheter of the same size The main principle consists in the

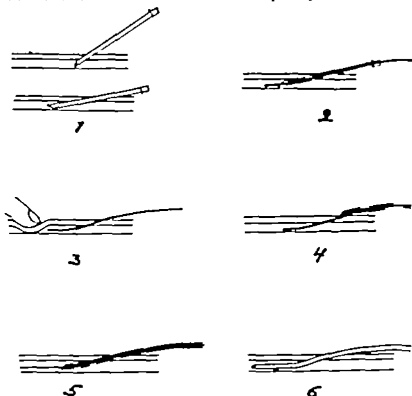


FIG 6. (1) Puncture of artery (2) Insertion of flexible metal leader (3) withdrawal of needle and digital compression of artery (4) polythene tubing threaded on to leader, and (5) passed into artery (6) leader withdrawn. (From *Acta Radiologica, Stockholm.*)

catheter being introduced on a flexible leader through the puncture hole after withdrawal of the puncture needle.

The Seldinger apparatus (Fig. 5) consists of a puncture needle and stilette a flexible rounded-end metal leader with increased flexibility of its distal 3 cm. and polyethylene tubing, the same outer diameter as the needle and which will fit freely over the metal leader

The technique as described by Seldinger (1953) is as follows (Fig. 6)

(a) After local anæsthesia, the artery is punctured percutane at a relatively small angle.

After puncture it is best to rotate the needle 180 degrees push it a little into the artery using the bleeding as a guide to er that the needle remains in the artery Puncture of arteries sm than the femoral artery is facilitated by using an inner needle guide over which the outer needle is directed into the artery

(b) The supple tip of the leader is inserted a very short dist into the lumen of the artery through the needle.

(c) The leader is held in place and the needle removed."

At this moment bleeding should be controlled by pressur the artery proximal to the puncture site, because the diameter o leader is smaller than the hole in the artery

(d) The catheter is threaded on to the leader when th reaches the skin the free end of the leader must protrude from catheter

" (e) The catheter and leader are gripped near the skin thro which they are inserted. The catheter enters the artery easily a opening has already been made by the needle. The catheter leader are pushed just far enough to ensure that the tip of the for is in the lumen of the vessel

(f) The leader is removed and the catheter directed to the l required, after good arterial bleeding through the catheter has t obtained The unsupported catheter is usually pushed up the ve without difficulty but occasionally the leader must be re introdu into the catheter in order to support it. The leader should no passed beyond the tip of the catheter

This technique is simpler than appears on paper and after a l practice should present no difficulties. It is important that leader passes into the artery easily When the tip of the cath enters the artery the same resistance is often felt as when punctu is performed by means of a needle. However the resistanc generally slight or may be completely absent. If consider resistance be encountered, it is probable that the tip of the lea is obstructed and force must therefore never be applied. P ethylene tubing is unfortunately not radio-opaque. For this reas in aortography via the femoral artery a small amount of cont

medium must be injected and followed by a test exposure This wi show the position of the catheter and also the exact situation of th renal arteries and of the iliac bifurcation (Seldinger 1953)

The actual film exposures are made in the usual way during th injection of 30 ml of 70 per cent contrast medium hand pressur on the syringe being sufficient in most cases

Many workers in this country have experienced troublesom extravasation at the site of femoral puncture with the result the direct puncture of the aorta via the lumbar approach continues t be the method of choice in Great Britain Although aortography i quite unnecessary in the majority of renal problems, its place in th diagnosis of the difficult or unusual case is now well establishe (Weyde, 1952)

Perirenal Insufflation

The injection of air or gas into the perirenal space in order t increase the radiological contrast between the kidney and surround ing structures dates back to the work of Rosenstein (1921) an Carelli and Sordelli (1921) who used oxygen for this purpose, bı since then various gases such as nitrogen carbon dioxide, and a have been used The original technique was modified by Cope an Schatzki in 1939 With the patient lying prone, some 200 ml ‹ air were injected through a long needle introduced in the ang between the crest of the ilium and the lateral border of the erecto spinæ thus avoiding direct injury to the kidney The best films wer frequently obtained eighteen hours later

All the earlier methods have now been superseded by the introdu tion of the gas into the retroperitoneal tissues lying in front of th sacrum and behind the rectum (Rivas, 1947) This is much easi to do accurately than the older methods since the needle, introduce just lateral to the coccyx, can be guided into place by a finger in th rectum. 1,000 ml. or more of oxygen can be used and both perirens spaces can be outlined at the same time. This is frequently a ver valuable asset particularly when trying to outline the suprarens glands, or when used in conjunction with excretion urography . satisfactory insufflation via the presacral route will also outline th pelvic viscera and in the author's practice this fact drew attentio

to a pelvic kidney which had already escaped detection by pyelography and aortography

Failure to obtain a sharp radiological outline of the kidney generally indicates adhesions and can be very useful in assessing the degree of operability in renal tumours as suggested by Riches and Griffiths (1951)



FIG 7 Urethrogram, showing chronic prostatitis three and a half years after a one-stage Freyer prostatectomy (From Marco Caine (1952) *Brit J Urol*, 25, 18)

Perirenal insufflation should not be a routine investigation, but it has a very necessary place in the diagnostic armamentarium of the urologist. The presence or absence of a suprarenal gland can sometimes be verified by no other means. The problem of the radiologically non functioning, and therefore possibly absent kidney though considerably helped by aortography can often be solved by a combination of excretion pyelography and air insufflation

Urethrography

Most British urologists would consider that cysto-urethroscopy can provide all the necessary information about the urethra and bladder neck in the great majority of cases so that the technique of urethrography has not become a routine procedure here to the extent that it has in Scandinavia However where instrumentation is impossible such as in cases of stricture or post-operative bladder neck obstruction (Fig 7) urethrography can be invaluable, provided

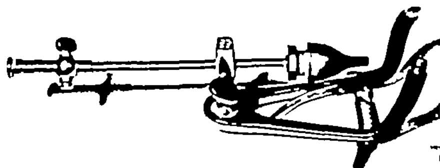


FIG 8 Knutsson penile clamp and urethrogram syringe.

the technique is such that the resultant radiographs do represent the true anatomy or pathology and are not due to artefacts

A reliable technique has been developed by Knutsson (1935) and others and consists essentially in filling the urethra with opaque medium and obtaining radiographs in various planes. The use of a syringe with the special Knutsson penile clamp is almost essential if adequate urethral filling is to be obtained (Fig. 8) By this means the urethra can be kept distended for several minutes in complete comfort, a fact which allows the use of water-soluble media such as visciosol instead of thick oily substances which may give false shadows due to urine droplets

Micturating Urethrograms

If the bladder is filled with opaque medium and films exposed during the act of micturition useful information can sometimes be obtained about bladder neck dysfunction although the results are difficult to interpret (Edling, 1945)

Seminal Vesiculography

The urethroscopic catheterisation of the ejaculatory ducts in order to obtain a vesiculogram is a challenging technical manœuvre which



FIG 9 Descending vesiculogram showing large cyst of left seminal vesicle. (Hanley (1955) *Ann Roy Coll. Surg Eng.*, 17 11)

requires much skill and patience, and above all luck. The necessity for so much of the last factor makes it too unreliable to become a useful routine investigation.

Very adequate radiological definition of the vesicles can be obtained by injecting medium down the vas from a scrotal incision (Fig. 9) but here, again it is doubtful whether the procedure can give any new useful information which cannot be obtained by other means and its routine application must be very limited

Pyelography in Infants

Excretion urography in infants may present insuperable difficulties owing to the small size of the veins In such cases diodone solutions can be injected intramuscularly It has recently been shown (Olsson and Loefgren 1949) that hyaluronidase if mixed with the diodone will increase the rate of absorption from the tissues particularly if the injection is made subcutaneously (Astley 1952) Fifteen ml of diodone solution and one millilitre of hyaluronidase divided into two injections will often produce satisfactory contrast in about the same time intervals as the intravenous route

Intestinal gas shadows are always a problem in infants, but they can sometimes be pushed aside by giving a Seidlitz powder which fills up the stomach with carbon dioxide thus producing one single bubble over the renal areas Tizer or any other sweet fizzy drink is even simpler to administer (Berg and Allen 1952)

The X ray Image Amplifier in Urology

The great advantages which would accrue from being able to visualise the actual movements of the renal pelvis calices, and ureter have been obvious to urologists since the advent of contrast media and the fluorescent X ray screen Many urologists perform their ascending pyelograms under screen control but although much valuable information can be obtained by this means, the small volume of opaque medium which can be used provides poor contrast as compared with a barium suspension in the bowel while the light intensity is insufficient to provide really clear definition of the calices.

The fluorescent screen can of course be made brilliant enough for clear definition and even for photography by greatly increasing the screening current and this is how the ordinaty excretion urogram film is exposed. A high screening current is used for a very short exposure. Unfortunately the X ray dosage absorbed by the patient during such an exposure is high and can be repeated only a few times with safety Up to the present time fluoroscopy and certainly ciné photography has been limited by this problem of having to choose between a low X ray dosage with poor illumination for a

reasonable length of time, or a high X ray dosage with brilliant illumination for a few seconds only

However this problem has now been solved by the use of an

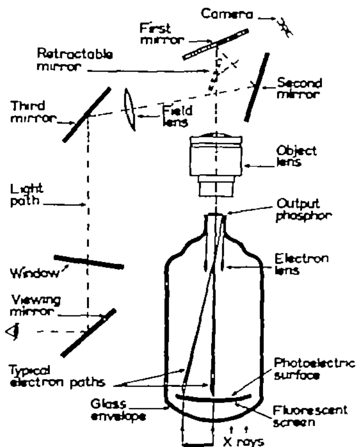


Fig. 10. Diagrammatic representation of the Marconi image amplifier showing path of electrons through tube, together with optical system of mirrors for visual screening. The retractable mirror which is of a semi-transparent nature, is used to reflect some 90 per cent of the light into a 16 mm. ciné-camera while still allowing the operator to see what is being photographed. (Hanley (1955) *Brit med. J.*, 2, 22.)

X ray image amplifier which, as its name implies, amplifies a poorly illuminated screen image by electronic means (Fig. 10) The instrument is attached to an ordinary X ray apparatus in place of the usual

viewing screen so that the X rays strike a metal screen inside an evacuated glass tube Instead of producing a fluorescent image this screen emits electrons which are greatly accelerated through the tube by a potential difference of 25 kV., and are kept in focus by several "electron lenses" until they strike a small 1 in (2 5 cm) fluorescent screen at the other end This is similar to an ordinary fluorescent



FIG. 11 Stills from a ciné-pyelogram. The ureteric catheter has been withdrawn after filling the pelvis with opaque medium.

FIG. 11 (a). Shows a well-filled lower calyx and a clearly defined pelvi-ureteric junction which has just closed above a column of medium in the ureter

viewing screen except that the image is reduced in size to 1 in., but is extremely brilliantly illuminated An optical system can now project this image either through an eye piece, on to a mirror system or of greater importance still into the lens of a ciné-camera.

A bright visual image of the renal shadow can be seen with a screening current as low as a half to one milliampere, while ciné radiography can be carried out with a current as low as 6 to 7 milliamperes in some cases (Hanley 1955)



FIG 11 (*b*). Two seconds later The neck of the middle calyx has closed. The lowest calyx is emptying into the pelvis while the " column " of medium in the ureter is moving downwards.



FIG 11 (*c*). One second later still. The ureteric column is moving out of sight.

Using one of the new rapidly excreted opaque media such as Hypaque, with its radiologically denser molecule the slow movements of the calices can be clearly seen during excretion urography

It has already become evident that the interpretation of some of the unexpected phenomena which we are now seeing will require time and experience before their full significance can be assessed but the potentialities appear great (Fig. 11) particularly in the study of hydronephrosis ureteric spasm aortography and such problems of rapid muscular action as the micturating cystogram and ureteric reflux (Hanley 1955)

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CHAPTER 4

CONSERVATIVE RENAL SURGERY

Hydronephrosis

THE most important advances in renal surgery during the past fifteen years or so have been due to a change of outlook on the part of surgeons—particularly urologists, so that today the emphasis is placed on conservatism. The attitude that if the patient has another healthy kidney a nephrectomy is the best treatment for serious pathology thereby effecting a permanent "cure," is now largely frowned upon. Most urologists agree that with certain reservations, even a small portion of a poorly functioning kidney is better than no kidney at all, particularly in young people. The majority of renal disease is potentially bilateral, though one side may be affected much sooner than the other and the realisation of this fact has done much to stimulate interest and research in conservative principles particularly in hemi and partial nephrectomy and in plastic operations for hydronephrosis.

The success attained in such surgery has of course been helped by the factors which have contributed to advances in surgery in general, such as earlier and more accurate diagnosis, improving anæsthesia and the control of urinary and other infection, but of equal importance has been the determination of urologists to follow up their cases for a sufficiently long time and to learn from earlier failures.

We now know that the majority of hydronephroses encountered in practice are well worth saving, and there are several large series which have been followed over a period of many years.

At one time it was thought that the preservation of a hydronephrotic kidney might lead to hypertension but there is no evidence that this is so. No hypertension has developed in any of the author's cases over the past fifteen years, and this is supported by the Great

Ormond Street series, many of which have been followed up into adult life (Higgins, Williams and Nash, 1951)

Several points of interest should be noted about hydronephroses in general. The development of the condition is insidious in most cases and, unless attacks of infection occur symptoms may be late and vague. These symptoms only rarely point to the renal tract in the early stages and many cases seen by the author have already had barium meal examinations and cholecystograms. For this reason a high proportion of hydronephroses are first seen by the physicians or general surgeons, and if the latter are not interested in renal surgery a nephrectomy is the result.

Once a hydronephrosis has produced sufficient symptoms to call for investigation, it is generally a progressive lesion, and although early cases may be kept under observation for several months, some intervention becomes necessary eventually Once infection has developed there is little time to be wasted with chemotherapy or antibiotics

The *diagnosis* can always be made by excretion urography particularly on a delayed film, but if the ureters are not outlined the exact location of the obstruction will often call for the passage of a ureteric catheter to exclude lower tract of ureteric obstruction.

It should be remembered that a retrograde pyelogram will only rarely indicate the actual cause of the pelvi ureteric blockage, and gives little indication of the type of operation which will be necessary for its relief Also it cannot be stressed too emphatically that retrograde pyelography is a dangerous procedure in cases of hydronephrosis unless carried out just prior to operation because the mere passage of the catheter through an obstructed or œdematous pelvi-ureteric junction will increase the œdema and may result in a complete blockage, with rapid onset of infection and perhaps irreparable damage to the kidney It follows, therefore, that the retrograde pyelogram should only be performed by the surgeon, who is prepared to carry on and perform a conservative operation if necessary

It is claimed that *abdominal aortography* (p 51) is helpful in defining the presence and size of polar vessels thus making retrograde pyelography unnecessary while Doss (1947) and Weyde (1952)

have demonstrated that a good renal vascular pattern indicates the presence and amount of parenchymal tissue, thus justifying conservative surgery even if the excretion pyelogram shows poor function

Non-mechanical Hydronephrosis

This term was used by Oldham in his Hunterian Lecture (1950) to describe the case where no mechanical obstruction could be found at the time of operation More than half of Oldham s cases of hydronephroses fell into this category and although this incidence is far higher than that recorded by anyone else possibly due to a difference of interpretation as to what constitutes obstruction there is no doubt that on occasion one is confronted at operation with a perfectly normal pelvi ureteric junction and a collapsed even spastic pelvis when the pre-operative pyelograms had demonstrated a fully blown pelvis with delayed emptying.

Much work has been done on this subject but it is a fact that our knowledge of the nervous control and physiology of the passage of urine from the glomeruli to the exterior of the body is still beset with contradictions The pyeloscopy work of Harris (1930) Jona (1937) and the more recent work of Johnson (1952) using a Sanchez Perez automatic seriograph which gives eight films at timed regular intervals, has helped to throw some light on the problem but the introduction of cineradiography for urological purposes (Hanley 1955) should greatly increase our knowledge of pelvic dynamics

Physiologically there would appear to be sphincters at the junctions of the minor and major calyces and at the pelvi ureteric junction and Woodside (1944) pointed out that each segment of the calycine system filled up and then passed its contents into the next chamber Johnson (1952) supports Lapides (1948) contention that this action results from the mechanical pressure of the urine in each segment and is independent of any central control. However many people consider that the atonia seen in some calyces or renal pelves is due to inhibiting neuro-muscular impulses which prevent the sphincters relaxing, and this theory forms the basis of renal pedicle sympathectomy for cases of non-mechanical hydronephroses

Oldham s series of twenty-five well-defined hydronephroses

treated successfully by a thorough pedicle sympathectomy and, let it be admitted a careful pelvi ureterolysis is impressive. Having cut all the nerve fibres running along the arteries he then paints the vessels with 10 per cent phenol, pointing out that quite apart from the destructive effect on the sympathetic fibres, this makes them white and more easily visible.

Hydronephrosis due to Pelvi-ureteric Obstruction

Once a hydronephrosis of this type is well established with marked clubbing of the calyces no form of treatment will return it to normal, but a successful conservative operation should halt the progressive nature of the condition, improve the emptying time of the pelvis and eliminate infection and pain. Success cannot be gauged merely by comparing the size and outline of the pyelograms before and after operation since even after extensive resection of the pelvis the radiological outline may not appear much smaller whilst the calyces may still be clubbed but the emptying time should be greatly reduced.

Forms of Treatment

Well over thirty different surgeons have given their names to various operations for relief of obstruction at the pelvi-ureteric junction but until quite recently all these operations could be put into three main groups

Group 1 consisted of a careful ureterolysis That is to say a simple freeing of all adhesions fibrous or vascular round the pelvi ureteric junction This may be combined with a nephropexy or a sympathectomy but the pelvis and ureter are not opened.

Group 2 consisted of a ureterolysis combined with some form of incision of the stenosis followed by transverse or inverted U closure. Such names as Heineke Mikulicz, Finney and Foley (1937) spring to mind

Included in this group is the lateral anastomosis of ureter to pelvis below the site of obstruction, Priestley (1939) (Fig. 12 C)

Group 3 consisted of the ureterolysis and re implantation of the ureter into the pelvis at a more convenient site with or without

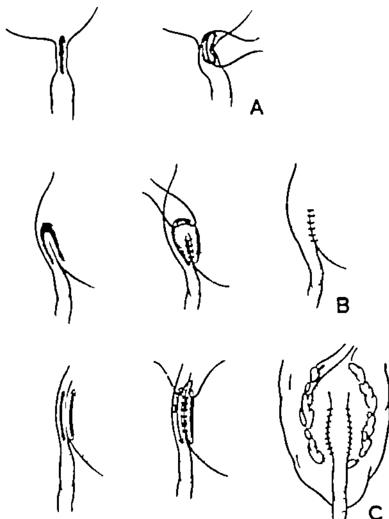


FIG 12. A. Simple incision with transverse closure based upon the Heineke Mikulicz pyloroplasty and described by Fenger in 1894 B. Curved incision with closure based upon the Finney type pyloroplasty C. Lateral anastomosis of ureter to pelvis for cases of high insertion of ureter (Priestley 1939).

resection of redundant pelvis. Kuster (1892) Lubash (1937) are suitable examples (Fig. 14)

It is difficult on occasion to appreciate the very slight differ ences in technique and nomenclature separating some of these

operations and also to decide whose name should be applied to them but Hinman (1946) and Gibson (1945) have done a service to urology by attempting to summarise the subject in two very comprehensive papers

Most urologists would now consider that a careful and thorough dissection of the pelvi-ureteric junction is one of the most important steps in any operation for hydronephrosis and while it is very doubtful whether these fibrous or vascular adhesions were the original cause of the condition, their removal is essential in order to obtain a normal alignment of the uretero-pelvic junction.

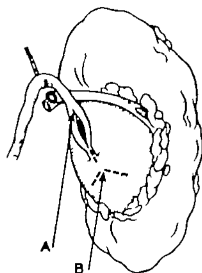


FIG. 13 Foley "inverted Y" incision (1937) Closure by suturing A to B.

In spite of the work of Lapides (1948) and Johnson (1952) who consider that the only relationship between a urinary segment and the one above it depends on the mechanical transference of fluid pressure, and not on any neuro-muscular or peristaltic wave, many urologists think that there is a nervous relationship and that for this reason the section and re-implantation of the ureter into the pelvis is an unphysiological procedure.

Certainly the majority of operations devised in recent years have aimed at avoiding re-implantation which has not been a great success in most people's hands but this may have been due to faulty technique There is little doubt that any operation involving a

circular scar round the ureter will lead to ultimate contraction and Anderson and Hynes (1949) have devised an operation to prevent this happening by ensuring that the healing scar is oblique, not circumferential (Fig. 15) No ureteric splinting or nephrostomy

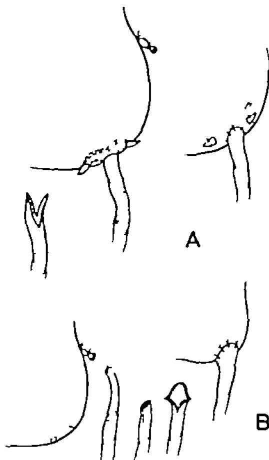


FIG. 14. A. Complete section with re-implantation after the method of Lubash (1937)
B. Re-implantation by Kuster s oblique method (1892)

drainage is employed and the authors consider that this lessens the degree of infection and fibrosis For high insertion of the ureter with a contracted pelvi ureteric junction this operation is very satisfactory Where the pelvi-ureteric junction is already at the lowest point the Y or V plastic operations are not applicable without altering the renal axis and, in addition if the ureteric narrowing

extends over several centimetres, re-implantation may be impossible. Intubated ureterotomy is a suitable procedure for such cases (p 79), but in an attempt to cut down the length of time of the splinting

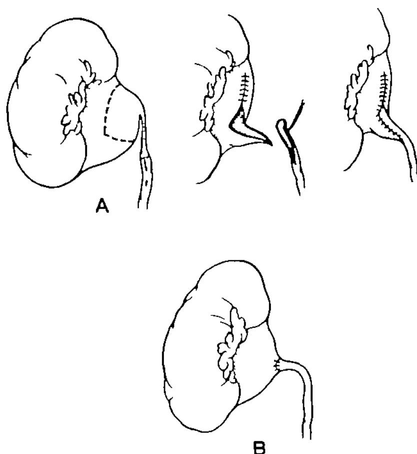


FIG 15 Anderson and Hynes operation (1949). Designed to avoid a circular scar which would result from a procedure such as that shown at B. No ureteric splint or nephrostomy is used.

Culp and de Weerd (1951 1954) have devised an operation suitable for this condition whereby a flap of pelvis is turned down to form a funnel-shaped pelvi ureteric junction and they have had good results in more than twenty-seven cases so far (Fig. 16)

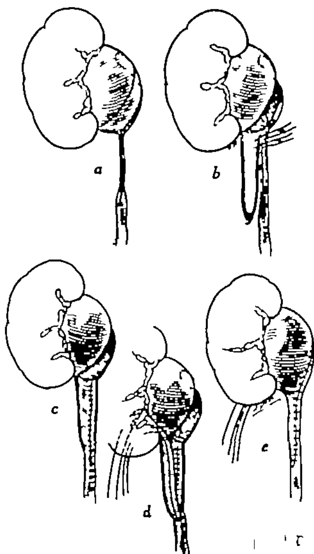


FIG 16. Culp operation.

(*a*) Location of incisions to create pelvic flap and to open the constricted segment of ureter
(*b*) Relationship of flap and open ureter
(*c*) One edge of flap and ureter joined by sutures.
(*d*) Position of nephrostomy tube and ureteral splint.
(*e*) Flap sutured to other edge of split ureter over the splint and defect in pelvis closed. (From staff meetings Mayo Clinic. Culp and De Weerd 1951 26, 483)

Whether polar vessels can be the initial cause of a hydronephrosis or not is still undecided, and it should be remembered that such vessels may not be the only cause of obstruction so that many urologists consider it essential to open the pelvis and test the patency of the pelvi ureteric junction (Henline, 1943)

However there is no doubt that once the pelvis is distended, such vessels, be they early divisions of the renal artery or true aberrant vessels, do prevent pelvic emptying, and though veins can be divided

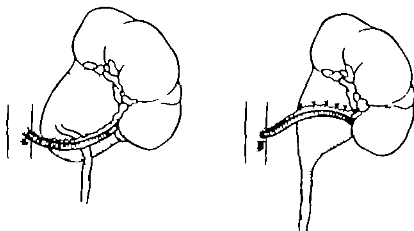


FIG. 17 Hellstrom procedure (1949) for transplanting an offending vessel away from the pelvi-ureteric junction. Only the perivascular tissue is taken up in the sutures.

with impunity arteries are a different problem small arteries may be safely cut, large one may certainly not, but the author considers that the borderline cases are very difficult and places little reliance on clamping and watching the effect on the lower pole.

One is faced, therefore, with the choice of dividing the vessels, re implanting the ureter or moving the pelvi-ureteric junction out of the way It is certainly surprising how often the ureter can be displaced from a vascular bundle by suitably resecting a portion of the anterior or posterior surface of the pelvis. Hellstrom (1949) describes good results in thirteen of fourteen operations for "transposition" of the offending artery by suturing its perivascular tissue to the renal pelvis in a position well away from the ureter (Fig. 17)

while Hamilton Stewart (1947) has devised an operation which aims in principle at "moulding" the kidney so that the lower polar or aberrant artery should come into closer relation with the renal artery itself where it would not be in a position to obstruct the ureter (Fig. 18) By manual moulding, the poles of the kidney are brought together reproducing the infantile state, and at the same time the anterior aspects of both poles, freed of capsule, are approximated and the resultant ball shape is maintained with ribbon catgut

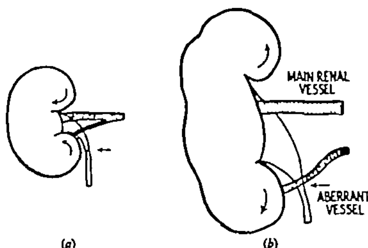


FIG. 18. Hamilton Stewart's conception of the changes occurring during the development and growth of the kidney (*a*) Shows the early stages where a polar vessel bears no relationship to the pelvi-ureteric junction. (*b*) Shows the opening up of the hilum during growth with the result that the polar vessel may obstruct the pelvi ureteric junction. (Reproduced by kind permission of the *Brit J Surg.*)

which encircles the whole mass like a hoop (Fig. 19) Any redundant pelvis is plicated at the front and back by interrupted 6/0 catgut, taking care that these sutures do not pass into the lumen of the pelvis This ingenious manœuvre overcomes most of the theoretical objections raised against previous operations for obstruction caused solely by aberrant vessels The offending vessels are not damaged, the pelvis is not opened thus avoiding infection of fistula formation while the functional results would appear to be very satisfactory

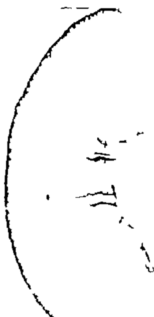


Fig 19 A.

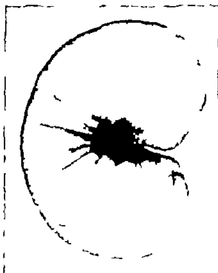


Fig 19 B



Fig. 19 C.



Fig. 19 D.

Fig. 19 Photographs of clay models illustrating the apposition of the anterior surfaces of the poles of the kidney so that adhesions may develop over a broad surface and retain the kidney permanently in its new shape (From Stewart, H. H. (1947). *Brit J Surg*).

Hamilton Stewart has now done over fifty such operations Wilfred Adams (1951) who prefers fascia lata to ribbon gut has recorded fourteen cases and other British urologists have reported favourably on the procedure.

Ureteric Splinting

Any or all of the principal types of plastic operation can be combined with ureteric splinting and nephrostomy drainage. The modern plastic types of tubing are much superior to rubber or to ureteric catheters since they rarely become coated in phosphatic concretions. The choice between pyelostomy or nephrostomy drainage is a personal one. The pyelostomy tube does no harm to the renal parenchyma but it is quite impossible to reintroduce should it come out by accident, and this has resulted in its diminishing popularity The advocates of nephrostomy or pyelostomy consider that it is the adequate drainage, rather than the meticulous suturing, which is the secret of success in any plastic operation In the same way it is argued that only an indwelling ureteric splint can ensure a smooth regular pelvi ureteric alignment following any type of anastomosis in this region In fact many urologists place so much reliance on the principle of splinting that they have abandoned most of the complicated Y and V flaps in favour of simple incisions or stretching of the ureteric junction followed by indwelling splintage

The principle of this intubated ureterotomy (Fig. 20) has been popularised by David M Davis of Philadelphia (1943 1948 1951) who has shown that in dogs and in man a tight or a long stricture of the ureter can be split longitudinally as in a Ramstedt operation for pyloric stenosis, and that even if the mucosa is deficient provided there is some continuity between ureter and pelvis a new mucosa will grow round an indwelling splint. Provided the splint is left *in situ* for sufficient time, the resultant fibrosis becomes stationary and further contraction does not occur the ultimate bore of the new ureter depending upon the diameter of the splint

This operation was originally used by Davis for a two-inch fibrous stricture, which after longitudinal division left only a thin ribbon of ureter This was loosely applied to the splint by interrupted sutures, surrounded with fat, and when the splint was withdrawn

six weeks later the structural deficiency had been repaired. The period of splinting necessary for this type of ureteric stricture is probably six weeks, but for a simple stenosis at the junction which

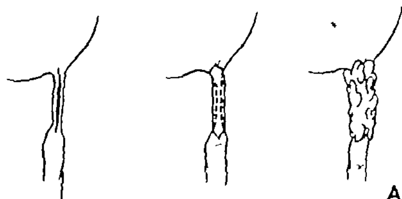


FIG. 20 A. Intubated ureterotomy Originally used by D M Davis (1943) for a long stricture below the pelvi-ureteric junction. The stenosed portion of ureter is stretched open from within the pelvis until a plastic splint of the required size will pass. No attempt is made to close any gaps in the mucosa resulting from this manœuvre, but they may be covered with a fat patch. At least three weeks are required for re-epithelialization during which time the splint and nephrostomy tube remain undisturbed.

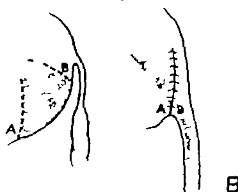


FIG. 20 B. High insertion of the ureter can be overcome by resecting a suitable portion of pelvis so that A. and B. are approximated.

has been split open at operation by bougies, the author has found that three weeks is adequate. Although even a shorter period may suffice, it would appear to be safer to splint for too long than too short a time. This principle of intubation is much simpler to apply

than any of the flap operations, and is more generally applicable to the various types of obstruction encountered A high insertion can be overcome by resecting a piece of pelvis and bringing the junction to the most dependent position (Fig. 20 B) This operation is certainly gaining in popularity doubtless due to its simplicity and the author has found it applicable to the majority of cases where there is a polar vessel too large to divide with safety

It will be seen that no single operative procedure is suitable for all of the various types of obstruction encountered while the fact that different surgeons prefer different methods for the same pathology indicates that the problem is still unsolved. Nevertheless, the results of conservative operations in hydronephrosis are now so greatly improved that nephrectomy should only be considered as a last resort.

Heminephrectomy and Partial Nephrectomy

The term heminephrectomy should be used for the removal of half—even an unequal half—of a double kidney while the term partial nephrectomy should be reserved for the various resection operations where a portion of parenchyma of a single kidney is removed for localised disease, including calycectomy and resection of cysts. Heminephrectomy is a well-established operation and is used chiefly for lesions which frequently develop in the poorly developed upper pelvis of a double kidney This pelvis may be hydronephrotic, it may contain calculi while not infrequently it may be a source of chronic infection or of renal pain. Crossed ectopic and horseshoe kidneys are included in this group, and all have in common the fact that the portion to be removed has a separate blood supply and often shows a clean line of cleavage so that bleeding is not troublesome.

True partial nephrectomy has remained unpopular until quite recent years owing to a mistaken idea that it was associated with much morbidity such as severe hæmorrhage and prolonged fistula formation. A review of over 150 operations performed by various British urologists (Hanley 1950) shows that there is in fact little morbidity Clot retention occurred in the bladder in twelve cases, but secondary nephrectomy was only necessary twice, while no

fistula lasted for more than a week. Only one death was recorded in this review

There is a growing volume of opinion that partial nephrectomy is the operation of choice where the disease is confined sharply to one area of a kidney and where the blood supply remaining is adequate to support the tissue left behind Calculi in the lowest calyx form the most frequent indication for polar resection since the recurrence rate after simple lithotomy is very high for various



FIG. 21 X-ray photograph of resected lower pole showing areas of diffuse calcification (From Mr T J Lane). (Hanley 1950. Reproduced by kind permission of the Proceedings of the Royal Society of Medicine.)

reasons, not least being the great difficulty of removing all the fragments at operation Lane (1950) has shown that even if all the gravel is removed the calyx is deformed and its lining membrane may be eroded and replaced with granulation tissue, while the parenchyma may show chronic intestitial changes with patches of calcification such as the specimen shown in Fig. 21

Wherever stones commence to grow they certainly tend to drop into and mature in the lowest calyx, so that resection of this calyx does at least remove the sump, with the result that any further stones tend to pass down the ureter while still small enough to do so Hamilton Stewart (1952) considers that even if a stone is wedged in a middle or upper calyx the mucosa and parenchyma are generally damaged, so that recurrence is likely unless the area is resected and,

adopting this theory he has reduced his recurrence rate after partial nephrectomy for calculi to 6 8 per cent in eighty seven cases. Incidently his six recurrences all followed lower polar resections where a minor calyx or a truncated lower major calyx had been left behind, and he rightly stresses the importance of removing the whole of the lower calycine system.

Tumours

Partial nephrectomy for simple tumours would be ideal if the diagnosis could be made with accuracy but even malignant tumours have been resected with success, under certain circumstances

Tuberculosis

Genito-urinary tuberculosis is only part of a generalised disease and it is now hoped that under ideal sanatorium and antibiotic control small non radiologically demonstrable lesions in the kidney will heal Only a few years ago it was equally certain that an established ulcerated cavity was most unlikely to heal under *any conditions*, so that if a lesion remained localised to one calyx and showed no radiological extension after a reasonable period of observation and conservative treatment a partial nephrectomy appeared to be justifiable However with antibiotic treatment carried on for several years it is often possible to keep the urine sterile in spite of a very obvious radiological calycine lesion and time may show that even partial resection is unnecessary in such cases.

It is too early to assess the final place of this procedure in genito-urinary tuberculosis but in spite of a cautious note by Cibert in France (1953) there are several growing series of cases under observation, notably those of Semb (1949 1955 1956) in Oslo Lattimer in New York (1953) and Ljunggren (1952) in Gothenberg, while in this country Jacobs in Glasgow Ross and Gow in Liverpool, and the author are encouraged to continue with this operation in suitable cases. Multiple resections on one or both sides have been carried out with success

Technique of Partial Nephrectomy

Very adequate exposure of the pedicle is necessary in order that the assistant can grip the vessels firmly without interfering with the

surgeon's view and approach. Some surgeons prefer to use a light rubber-covered clamp to control the pedicle, others use Pyrah's clips, but even here it is an advantage to release them periodically to demonstrate the main vessels which have been cut during the wedge resection. The larger vessels, all centred round the calyx in the apex of the wedge, can be ligatured by this means.

The opening into the pelvis can be demonstrated and, if adequately closed, the chances of clot colic or escape of urine into the wound are reduced.

The methods of hæmostasis vary but the most popular is probably Lowsley's (1933) method of using a fat plug which is placed in the wedge and held *in situ* by the capsule which has been preserved. A piece of muscle can also be used.

Deep mattress sutures are advocated by some surgeons, but the experimental work available would indicate that this may cause renal damage (Herbst, 1930) and in the same way diathermy for the excision is contra indicated (Yunck and Forsyth, 1941)

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CHAPTER 5

PROSTATIC OBSTRUCTION

Management of Retention

TODAY it would be impossible to lay down any fixed routine treatment for a case of retention which would be generally acceptable, and this fact alone indicates that the correct answer is not yet known. Out of the conflicting mass of opinion one fact certainly emerges no two patients or two prostates are alike and no particular operation is suitable for all cases.

Acute retention is probably still treated by indwelling catheterisation in most centres This is continued until the renal function tests and the excretion pyelography have been done, after which a one-stage prostatectomy is performed However most urologists try to reduce the time of catheter drainage to a minimum owing to the inevitability of some degrees of urethritis, with perhaps a troublesome narrowing in the region of the fossa navicularis. Many cases of acute retention occur in frail old men whose normal activities are suddenly limited by purely medical causes. Immediate prostatectomy is not the answer for these cases any more than is an indwelling urethral catheter and in such patients a Riches suprapubic catheter is ideal.

Riches Suprapubic Catheterisation

This procedure was devised by Riches (1943) for use in the spinal injury centre at Stoke Mandeville, and enabled a suprapubic tube to be inserted without opening up the prevesical space, thus avoiding the subsequent contraction and adherence of the scar to the symphysis. It differs from the ordinary stab cystotomy using a trocar and cannula in that the catheter is its own cannula (Fig. 53 p. 177) A long, thin trocar fits inside a special soft rubber catheter the tip of which is gripped by an ingenious knife-edged device, thus allowing the catheter to be stretched and reduced in diameter When

the distended bladder has been carefully defined above the pubis a half inch skin incision suffices to introduce the trocar and catheter into the bladder Release of the special catch enables the catheter to expand thereby making a water-tight union through the bladder wall and allowing the trocar to be withdrawn. A special advancer is used to push the catheter well inside the bladder so that as the latter empties and contracts the catheter will still remain *in situ* Scorer (1953) was the first to report a series of acute and chronic retention cases treated by this method with gratifying results. The procedure can be carried out in the patient s bed under a local anæsthetic, and he can then be allowed to walk about provided there are no other medical contra-indications This in itself is of great importance, since bed is probably the worst place for a frail old man No leakage occurs round these catheters, with the result that the cave of Retzius generally remains uncontaminated and a subsequent retropubic or any other prostatectomy can be performed easily

Chronic Retention

The management of this condition has undergone a change in recent years in that most urologists regard slow decompression of the bladder as unnecessary provided the patient s clinical condition is reasonably satisfactory and the blood urea is not unduly raised

The late Wilson Hey (1945) has shown that immediate prostatec tomy can be performed in these cases with safety However a difference of opinion arises over the patient with a markedly raised blood urea, a dry tongue and a lethargic appearance, or whose excretion urogram shows back pressure changes Wells (1952), and a number of like minded surgeons would decompress such patients suddenly and perform a prostatectomy regardless of these signs of uræmia, and the successful results obtained prove that in many cases it is a safe procedure. Nevertheless, a majority of urologists still treat chronic retention with great care and respect, and although only lip service is often paid to slow decompression a few days of bladder drainage by catheter or by any other means are generally advocated

In the author s experience it is not the failing renal function which kills such patients but the associated cardio-vascular and pulmonary

lesions, and these will improve considerably with a few days bladder drainage. Even so the set suprapubic cystotomy is rarely necessary and one-stage operations are now in vogue.

PROSTATECTOMY

In 1927 Harris described his technique for securing improved hæmostasis, with the accompanying advantages of primary bladder closure, but his work escaped notice by all but a few It was not until 1934 that British urologists showed interest in the Harris operation and, although it never became popular in America, it was used routinely by many urologists in this country for the next ten years or so In spite of this Freyer continued to be the most commonly performed operation in the country as a whole

During this time acute retention of urine in a relatively fit man was treated by catheter decompression, followed by prostatectomy after suitable preparation and evaluation of the renal function. Chronic retention was regarded much more seriously and slow decompression was carried out over a period of many hours. If the blood urea was raised a two-stage operation or at least a lengthy period of catheter drainage was called for and the resultant contraction of the bladder usually prevented the introduction of a Harris or any other retractor so that a Freyer operation had to be performed.

Perurethral resection of the prostate was used as a routine measure by certain British urologists at this time, but the procedure was never as popular as in America. Perineal prostatectomy was even less commonly performed, so that the writing of this chapter in 1944 would have been straightforward and would have contained little controversial matter

In 1945 two British surgeons Wilson Hey and Millin, introduced new operations which had the effect of causing a reassessment of the whole problem of bladder neck surgery Even surgeons who did not perform either of the new operations began to challenge the old dogmas, particularly with regard to the treatment of chronic retention by slow decompression while suprapubic cystotomy for so long the accepted preliminary treatment for the poor-risk patient, became

less and less popular giving way in some centres to immediate prostatectomy even in acute retention cases

The new operations of Wilson Hey and Millin were both equally revolutionary but in totally different ways Millin (1945) advocated a retropubic approach without opening the bladder but Wilson Hey (1945) though using the old transvesical approach advocated an aseptic operation which he claimed to achieve by immediate prostatectomy for acute or chronic retention regardless of the blood urea He asserted that immediate prostatectomy by decompressing the lower ureters, relieved the renal back pressure whereas a preliminary cystotomy or catheter drainage had no such effect but merely served to introduce infection. For this reason he forbade any urethral instrumentation including cystoscopy before operation.

Both of these operations dispensed with any suprapubic urinary drainage, and this drew attention to the fact that many more bladders could be closed primarily with safety than had been generally realised. Previously many surgeons had performed the Harris operation in detail up to the closure stage and had then left a suprapubic tube *in situ* but today primary bladder closure is becoming more and more popular not only after prostatectomy but after such procedures as partial cystectomy and the insertion of radon seeds or irradiated tantalum wire.

Retropubic Prostatectomy

Millin s retropubic operation (1945 1947) introduced a new extravesical approach to the prostate, and its many advantages, particularly from the point of view of the patient s comfort have made it the operation of choice for most urologists. It would be superfluous to try and improve upon Millin s own descriptions of this operation but the main steps are clearly shown in Figs. 22, 23 24 and 25 Apart from the transverse skin incision now used by Millin various modifications are practised or described, but it is doubtful if they have any advantages over the original technique. The lateral gauze packs may be dispensed with in most cases but two-layer closure of the prostatic capsule appears unnecessary if not impracticable, while a vertical capsular incision has a tendency to extend downwards under

the pubic arch and can be embarrassing. If this vertical incision is made higher up over the junction of prostate and bladder, the resultant vesico-capsular approach suggested by Ogier Ward (1948) gives a good exposure in cases of fibrous contraction of the

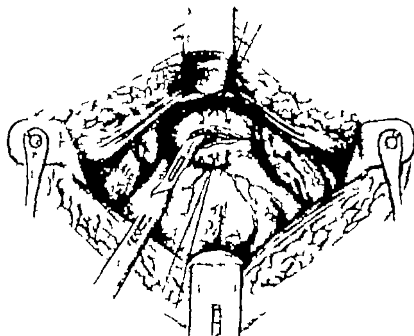


FIG 22. Retropubic prostatectomy The veins on the anterior surface of the capsule having been tied or coagulated, a transverse incision is made down to the adenoma, which can be seen glistening in the depths of the incision.

bladder neck which cannot for some reason be treated by endoscopic resection The author has found this approach useful in defining the prostatic urethra in infants with congenital valves.

There is no doubt that the retropubic approach is one of the greatest advances in prostatic surgery The patient has no supra pubic tubes he can get out of bed at a very early date his urethral

catheter is out in four or five days and normal micturition is restored immediately after this Dribbling may continue for a few days but is rarely prolonged

Radical prostatectomy can be performed by the retropubic route

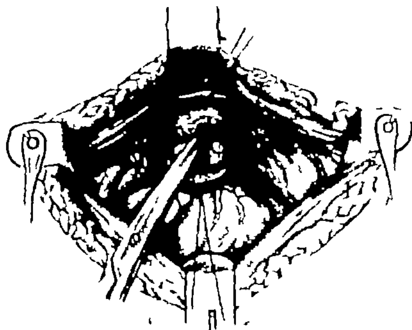


FIG. 23 Curved scissors are used to open up the line of cleavage between capsule and adenoma, and to divide the prostatic urethra at the apex of the adenoma if necessary Enucleation is completed by the finger

and will obviously be easier than the perineal operation in the hands of surgeons unfamiliar with the latter approach (Memmelaar 1949) Calculous prostatitis would appear to be the chief indication for total prostatectomy since other forms of surgery give only partial relief and Millin contends that the radical retropubic operation is

less likely to give incontinence, stricture or fistula formation than the perineal operation

However radical prostatectomy for early carcinoma is being performed in many American centres and the results are being

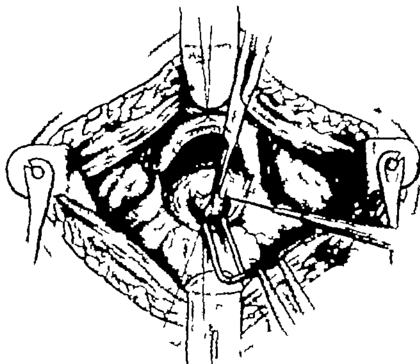


Fig. 24 When the adenoma has been enucleated, a deep wedge of bladder neck must be resected if post prostatectomy obstruction is to be avoided. Bleeding points can be clearly seen and coagulated.

carefully followed by all British urologists, who are not as yet convinced that the expectation of life is better following surgery than with oestrogen therapy Surgical success can only follow very early diagnosis and the comments on this subject under perineal

prostatectomy on p 94 are equally relevant to the retropubic approach, which in this country at least is likely to become the operation of choice.

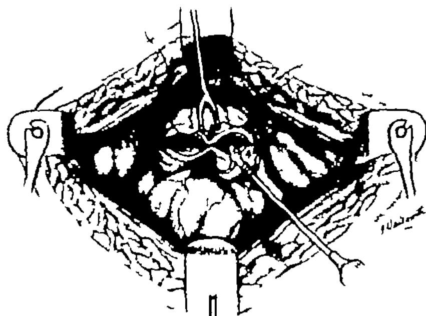


FIG. 25 The capsule is closed by a continuous catgut stitch inserted with a boomerang needle. The illustration shows the first central fixation stitch being applied. While this is not essential it defines the central point, and enables the subsequent continuous suture to be applied symmetrically thus achieving a water-tight junction. No attempt is made to sew up the capsule in two layers.

Wilson Hey Prostatectomy

Wilson Hey's operation (1945) is important not so much for any great variation in technique but because it has stimulated urologists to review the whole problem of urinary obstruction and to abandon some of the older misconceptions. To qualify for an aseptic prostatectomy no urethral instrumentation is allowed before

operation Even the grossly distended bladder is decompressed suddenly and the prostate is excised and enucleated by a modified technique which was adequately described by Hey (1945) and by Wells (1952) Hæmostasis is obtained by extensive diathermy coagulation of the whole cavity and the importance of removing any trigonal shelf is emphasised

The facilities for carrying out all Hey's requirements for an aseptic prostatectomy are granted to only a few surgeons. Catheterisation will already have been performed before admission to hospital in a high proportion of retention cases Emergency blood urea estimations and excretion pyelograms, followed by emergency prostatectomy operations have to be fitted into the general work of a hospital in most cases This upheaval could, and undoubtedly would be achieved if a sufficient weight of urological opinion considered it necessary, but at the moment this support is lacking except in a few centres.

Critics of the regime point to the necessity of cystoscoping a patient before removing his prostate However Hey's influence is shown here by the growing tendency to avoid cystoscopy until the patient is anæsthetised on the table ready for operation The increasing dislike of the urethral catheter as a preliminary drainage is shown by the tendency to perform one-stage operations even on patients with chronically distended bladders but, where retention is complete, most urologists consider that a night's sleep is more important for the patient than an emergency operation and they resort to catheter drainage until adequate preparations can be made.

Perineal Prostatectomy

The perineal approach to the prostate has never been popular in this country although, in theory the operation has many advantages Dependent drainage is obtained, there is little shock or hæmorrhage *and the mortality is low Against these must* be considered the occurrence of incontinence, which is notoriously difficult to treat, and a fæcal fistula, both of which may develop on occasion without apparent cause Stricture formation in the prostatic urethra and a perineal sinus are also unfortunate complications.

Total perineal prostatectomy has a place in the treatment of severe examples of calculous or fibrous prostates, but more especially in the carcinoma cases, where several five year cures are reported by Ormond (1947) and by Young (1945) who describes his prostato-seminal-vesiculectomy operation brilliantly

However it is important to realise that if a carcinoma has spread beyond the confines of the gland the survival rate with œstrogen therapy is as good as that following total prostatectomy A "cure" can only be obtained by removing the whole gland before the growth has escaped outside, and this requires very early diagnosis

Many papers have appeared recently in favour of early perineal biopsy of the prostate whenever a suspicious nodule is palpable per rectum. Such a nodule is inaccessible to a perurethral resection while punch or aspiration biopsies are not without morbidity and again, may fail to remove the suspicious area An open perineal exposure of the gland, however enables the actual nodule to be palpated and removed for section. Should this prove to be a carcinoma immediate total perineal prostatectomy can be carried out

This routine is advocated by many American urologists including Culp (1951), who stresses the fact that such an operation is only called for in cases with small localised nodules, without evidence of bony or other metastases, with a normal serum acid phosphatase, and in men whose expectation of life would normally exceed the prolongation provided by œstrogens It is safe to say that few urologists see cases early enough for radical prostatectomy and this is undoubtedly a tragedy since the only cures recorded so far have followed total prostatectomy For this reason Culp's plea for a perineal biopsy of any suspicious prostatic nodule may not prove so unreasonable as it appears to be at the present time

Coccyperineal Approach to the Prostate

A semi lateral approach to the prostate has been tried in several continental clinics, and the problem is reviewed by Couvelaire and Bouffard (1951) They describe their right coccyperineal route which they use for very fat men in whom endoscopic resection is contra indicated. This operation they claim avoids the complications of the

classical perineal approach by going round instead of through the central point of the perineum.

This operation is not performed in Britain.

Perurethral Prostatic Resection

This is discussed in Chapter 6

Local Hæmostatic Agents

The uses of absorbable gauze or other substances to promote hæmostasis in the prostatic cavity have been fully explored and reported in the literature. Vries and Buchanan (1947) attached strips of oxidised cellulose round a Foley catheter Gelfoam was used by MacDonald and Powell (1947) while Wells (1952) stresses the importance of using a substance which will fragment rapidly after removal of the catheter thus avoiding retention. He recommends Gelfoam soaked in thrombin solution laid on the floor and walls of the cavity after a Wilson Hey prostatectomy and held in place by a packing of Oxycel

Such ancillary methods of hæmostasis are not popular with British urologists.

Osteitis Pubis

Clinically this condition develops from two weeks to several months after prostatic or bladder surgery and is characterised by severe pain over the pubis, made worse by palpation or movement of the bony pelvis and referred to the perineum and inner sides of the thighs like an obturator neuritis. The typical X ray changes are late in appearing and can thus confuse the diagnosis, while the symptoms have abated long before the radiological changes show resolution in the form of recalcification and perhaps fusion of the symphysis pubes.

The exact pathology is still unknown in that it does not resemble a true osteomyelitis with alteration of trabecular structure and sequestration. Nevertheless chronic inflammatory changes are present and the accepted view is that infection is responsible for its development

The subject has been fully reviewed by Henderson (1950) who

agrees with Yates Bell (1947) that a low grade pelvic cellulitis secondary to prostatic infection produces a periostitis of the pubes. This may subside in a day or so but if it does not the periostium and fibro-cartilage of the symphysis are destroyed and bare bone may be palpated with a probe if a sinus develops He considers that the later X ray changes are due to the hyperæmia

Osteitis pubis occurs chiefly in patients whose bladders have been opened, but is by no means confined to this group The first case was probably described in 1827 by Elliotson following a prevesical abscess in a female but attention was refocused on the condition at the time of the introduction of retropubic prostatectomy and this led certain people to regard it as a particular complication of this operation In actual fact minor degrees of osteitis pubis occur more often than we realise after various bladder operations and many cases have passed unnoticed or at least undiagnosed, in the past.

One of the largest series comes from Mortensen (1951) who collected 48 cases from sixteen of his colleagues of the Urological Society of Australia 29 of his 48 cases followed retropubic prostatectomy while only five followed transvesical prostatectomy but these figures are not statistically significant unless we know the relative numbers of retropubic and transvesical operations per formed

In Henderson s review (1950) of 64 cases in the literature up to 1948 39 of them were before the retropubic era of 1945 while none of the 7 cases reported by Lavalle and Hamm in 1949 or the 7 cases by Beach in 1949 followed retropubic operations. The 4 new retropubic cases collected and described by Henderson were all treated with catheter drainage.

In the author s experience of four cases two followed retropubic prostatectomy with preliminary catheter drainage, one a Harris operation preceded by prolonged catheter drainage, and the fourth followed an indwelling catheter for a urethral stricture No further case has occurred during the last ten years and the only alteration in technique has been the abolition of pre-operative catheter drainage in favour of a Riches cystotomy The case against retropubic prostatectomy *per se* would appear to be not proven, and the many obvious advantages of the operation more than compensate for the

occasional occurrence of osteitis pubis, which it should be remembered has not been encountered at all by many surgeons

Treatment

In spite of the antiquity of this pathology treatment has remained largely ineffective and is chiefly symptomatic. Local heat may relieve the pain but physiotherapy in its widest sense gives little lasting relief The sulphonamides and antibiotics, though useful in cases of frank suppuration, do not alter the course of the disease, *while rest or immobilisation appear equally unhelpful* Deep X ray therapy is reported to be of value according to Beech (1949) but the results do not appear to be very dramatic and are difficult to assess.

More recently Marshall (1952) and his colleagues found that the administration of ACTH gave dramatic relief to two patients, and limited relief to a third. Nugent (1953) found that 50 mgm of cortisone every four hours gave almost complete relief to his patient, but that any marked reduction in this dosage was followed by relapse. Therapy was continued for four months, the dose being adjusted by the patient according to his needs until he finally became symptomless

Apart from the relief of the symptoms, no alteration in the course of the disease was noted

Prognosis

The condition is self limiting and generally lasts from four to six months, but some discomfort on walking may be present for a year or more.

Periurethral Resection, p 100.

Carcinoma of the Prostate, p. 113

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CHAPTER 6

PERURETHRAL PROSTATIC RESECTION

by

T L. CHAPMAN

PERURETHRAL resection of the prostate is now accepted as a standard surgical operation. Its precise place in the treatment of prostatic disease varies in different clinics, but that it has a place is no longer questioned.

From the beginning two distinct types of operation have developed. In the one, tissue is "punched" out by a tubular knife and hæmorrhage is controlled by a diathermy electrode. In the other tissue is excised by a cutting current applied through a sliding wire loop Developments continue along those two lines

Excellent results have been achieved by both methods and large series have been reported from America where both methods originated. The commonest practice in Great Britain is to restrict perurethral resection to a moderate proportion of prostatic cases, especially fibrous and malignant prostates and the smaller examples of benign hypertrophy and to use the loop type of instrument. In a few clinics perurethral resection is applied to a higher proportion of cases, and in these the punch instrument is the more popular Considerable series have been reported with low mortality (Stewart, 1945 Lane, 1949 Chapman and Sutherland, 1952) The choice of instrument depends chiefly on early training and personal inclination. Advances in recent years have increased the speed of the operation and reduced the incidence of complications.

Vision in the Two Types of Resectoscope

In the loop instruments vision is by a foroblique telescope in the "punch" instrument direct vision is employed. Both of these instruments give a view which is different from the right angled lens

to which most British urologists are accustomed The difference is less marked in the case of the foroblique lens and that is probably the chief reason for the greater popularity of the "loop instruments in this country The direct vision instruments show only a small field at one time and more movement of the instrument is necessary The vision is very clear however even in the presence of hæmorrhage. The operator looks through fluid which is just entering the bladder Tolson s instrument (Tolson 1946) combines a punch type of resectoscope with a foroblique lens telescope.

One-handed Instruments

McCarthy (1931) introduced the first popular form of the cutting loop instrument and numerous modifications have followed The Braasch Bumpus Punch was the first of this type to have a wide application in prostatic disease. Gershom Thompson s instrument was developed from it and became the most popular punch resectoscope. It has been recognised for a long time that useful help might be obtained at certain stages of the operation from the upward pressure exerted by an assistant s finger in the rectum Reed Nesbit (1939) introduced a form of the cutting loop instrument which could be used with one hand, allowing the operator to use a finger of the other hand for rectal pressure. Nesbit s original instrument had a pistol grip, but his more recent type (Nesbit, 1950) is designed for finger tip control The main feature of this more recent model is the introduction of roller bearings which improve the smoothness of movement. J Inglesias de la Torre (1948) devised an instrument which has two rings on either side of the sheath and a third ring which controls the movement of the loop The movement is similar to that of a syringe and is therefore a familiar one to all surgeons.

Efforts have been made to produce a one handed form of Thompson s instrument. Swinney (1954) has devised a thumb grip which rotates with the instrument (Fig. 26) It is set at a slight angle which permits good control throughout the full range of rotation The writer has found Swinney's instrument easy to use and a convenience even when a rectal finger is not necessary Sheppard s

instrument (Sheppard, 1952) is more cumbersome but can also be used effectively with one hand.

When these instruments are used the lower part of the patient's body is covered by a sterile rubber sheet which includes a finger

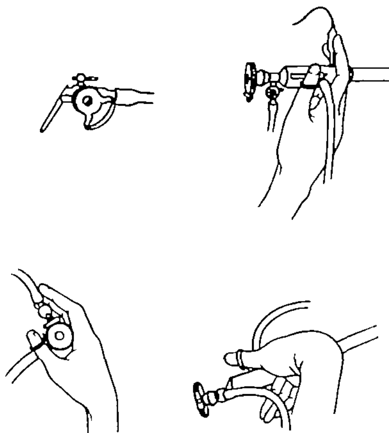


FIG 26. Swinney's modification of Gershom Thompson resectoscope.

stall. The use of the surgeon's own finger in the rectum gives greater co-ordination. The progress of the operation can be assessed with ease and the position of the last remaining piece of tissue is more readily determined. Mobile tissue is made more stable, and tissue which lies deep in the prostatic cavity is moved into a suitable position for resection.

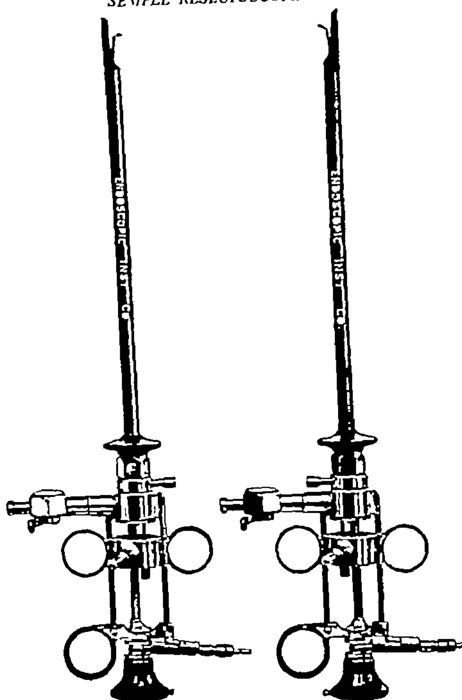


FIG. 27 Semple Rotating Resectoscope (Endoscopic Instrument Co. Ltd.)

Rotating Instruments

Several loop resectionists " have been impressed by the advantages of an instrument in which the sheath loop and lens might be rotated without changing the position of the operator s hands or of the water light and diathermy connections An instrument of this type was devised by Scott (1947) and has a grip of the pistol type. Semple (1952) produced the first British rotating instrument (Fig. 27). The grip is of the three-ring type like a local anæsthetic syringe. Another British instrument, the Schranz resectoscope (Fig. 28), has

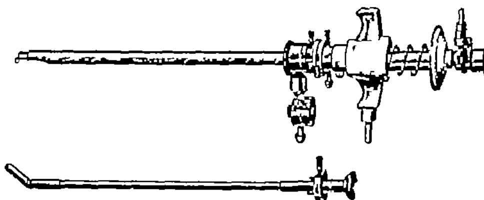


FIG. 28. Schranz Rotating Resectoscope (G U Mfg. Co Ltd.).

a light spring encircling the shaft between the fixed and moving parts By this means the loop is returned to position automatically after each piece is resected. The efficiency of this instrument is increased by fitting a water inflow tube of larger bore than the original one (Jacobs, 1953 personal communication). These instruments facilitate the operation especially in the anterior part of the gland—always a difficult region They also avoid confusion from entanglement of the various leads

Irrigating Fluids

In 1948 several American writers (Griffin 1948 Creevy 1948 Nesbit and Glickman 1948) described a risk resulting from the use of water as an irrigating medium in perurethral prostatic resection.

It is believed that water may enter the prostatic veins during the resection and hæmolysis has been demonstrated in a considerable proportion of cases. This hæmolysis is considered responsible for post-operative oliguria and anuria Various isotonic and nearly isotonic fluids have been recommended instead of water 4 per cent glucose and 1 1 per cent glycine are the most commonly used In many centres this precaution is not considered necessary The writer is convinced of its value. In his early experience several cases of post-operative anuria occurred—the incidence was about 1 per cent. Since 4 per cent glucose was first used as irrigating fluid over 1200 cases have been treated and no case of anuria has occurred

Introduction of the Instrument

Force of any kind must be avoided in introducing the instrument It must pass along the urethra by its own weight In the writer s experience this will occur in the majority of cases, provided that a full series of well-lubricated sounds is passed first of all The effect of this is probably to smooth out folds of mucous membrane and spread the lubricant thoroughly There is no active dilatation of the lumen. It is only rarely that the sound is gripped by the urethra. Stenosis of the external meatus, even of slight degree should be treated by meatotomy This is performed simply by crushing the tissue at the ventral margin of the meatus between pressure forceps and cutting through the crushed tissue with scissors.

When the urethra will not admit a resectoscope easily perurethral prostatic resection is still possible through the perineum. A small incision in the bulbous urethra will admit the instrument and from there it usually passes with ease into the bladder In the writer s experience the urethral fistula has been easy to close, but subsequent ureterograms have shown irregularity and in one case a stricture developed The closer proximity to the prostate does not facilitate the operation so much as might have been expected.

In order to negotiate the narrower urethræ instruments of smaller size have been made. The 1950 Reed Nesbit has sheaths of three sizes—24 26 and 28 F

Operative Technique

It cannot be claimed that any standard method of resecting prostatic tissue has been established but certain general principles are recognised. The intravesical tissue must be resected before the intra urethral. Bladder neck fibres should be exposed throughout their circumference and, in benign cases, the hypertrophied tissue should be completely or almost completely resected. The verumontanum is the landmark for the distal limit of resection. This rule is a safeguard against damage to the external sphincter The position of the sphincter itself can be identified, and Reed Nesbit (1951) has

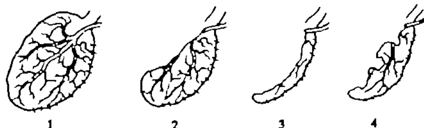


FIG 29 Blood supply of hypertrophied prostate.
1 Before resection.
2 After exposure of bladder neck.
3 Adequate resection.
4 Inadequate resection.

described a constant fold in the mucosa which is produced by movement of the prostate and which marks the junction of prostatic and membranous urethra. Flocks (1938) has shown that the lobes of a hypertrophied prostate obtain their chief blood supply from vessels which enter at the bladder neck Numerous small vessels pass through the capsule at various points but these only supply the extreme periphery of the gland (Fig. 29 (1)) The removal of the *intravesical part of a lobe exposes the bladder neck fibres. The main* vessels to the lobe are divided and coagulated. Thereafter the resection of the lobe is relatively avascular (Fig. 29 (2)). An adequate though not necessarily complete resection will leave only tissue which can be supplied by the capsular group of vessels and good healing will follow (Fig. 29 (3)) An inadequate resection will leave masses of tissue which have been deprived of their blood supply (Fig. 29 (4))

—an explanation for the poor functional results and severe post operative infection experienced by the imperfectly trained resectionist.

Different features are noted in the resection of fibrous, carcinomatous and adenomatous prostates In the fibrous gland the tissue is firm and is easily engaged Good function is usually established by the removal of only a small quantity of tissue. The tissue is also easy to engage in a carcinoma and blood loss is in general, very small. In the adenomatous type the tissue is more mobile and therefore less easily engaged This mobility should be turned to the operator s advantage The resection of the lateral lobe of an adenomatous prostate should begin with the removal of tissue from its anterior part until bladder neck fibres are exposed This will allow the lobe to fall towards the midline. The instrument may then pass above it, and the rest of the resection is simplified This is an important and useful manœuvre. With the punch instrument however it can be overdone, and elusive, wobbly masses of tissue may be produced. This danger appears to be less with the cutting loop resectoscopes

It is sometimes stated that the ideal case for perurethral resection is the fibrous prostate or the carcinoma in need of palliative relief of obstruction It is true that there is no good alternative in these cases, but it is not true to say that these are the easiest cases to treat or that they have the most satisfactory results. In the fibrous and carcinomatous prostates there is no clear limit to the operation and the operator must judge when he has produced a satisfactory channel. In the adenomatous gland however there is a clear differentiation between glandular tissue, bladder neck and capsule. The limits of the operation are well defined The easiest case for the beginner is the small adenomatous gland.

Suction Drainage

Keller Doss (1948) has described a suction apparatus which has reduced the duration of punch operations very considerably In this operation the bladder is alternately filled and emptied During the filling phase examination, resection and hæmostasis are carried out. The emptying phase, when slow was a great waste of time.

The suction apparatus not only reduces this time very markedly but also removes the cut tissue from the bladder without any effort by the surgeon and keeps the field clear of blood clot. The writer has found this method of great value. Although over 90 per cent of cases of prostatic obstruction are treated perurethrally the average operating time is about thirty minutes The collecting bottle is air tight and is fitted with two tubes one passing to the outflow of the instrument, and the other to a suction apparatus which maintains a negative pressure. Unless collecting bottles of very large size are used it is necessary to change them in the course of the operation.

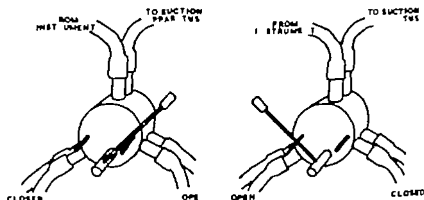


Fig 30. Chapman's device for easy exchange of collecting bottles.

The device shown in Fig. 30 has been useful With the lever in the first position one bottle is connected to the suction apparatus and to the instrument. When this bottle is full a single movement of the lever transfers the connections to the second bottle and there is ample time to empty the first one and collect the excised tissue while the second bottle fills.

Hemostasis

Post-operative instillations and irrigations with sodium citrate have been used by many surgeons with the object of preventing clot formation. The opposite approach was suggested in 1945 when instillations of thrombin were used. Routine post-operative irrigation of the bladder was given up at the same time and an easier

Post-operative stricture occurred in 2 per cent of cases and appeared to be more closely related to trauma than to urethritis. Perurethral resection should never be used unless the instrument passes with ease The urethra should be thoroughly lubricated and on no account should pressure be exerted on the instrument through the penis in order to engage tissue.

Incontinence of urine was the most common complication of importance, but was usually of short duration Permanent incontinence in a case of benign hypertrophy is very rare indeed.

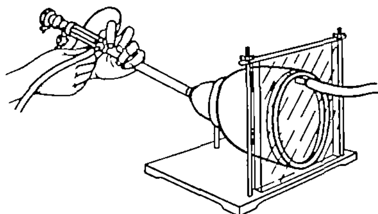


FIG 31 Model for demonstration and practice in punch resection of prostate.

On the whole the results justify the use of this operation and an extension of its use

The chief objection to perurethral prostatic resection is still the difficulty in learning the operation. The "apprentice resectionist" must learn first of all to recognise the landmarks of the operation and to distinguish easily prostatic tissue, bladder neck fibres and capsular fibres This is not difficult but it can be learned only by actual demonstration. At a later stage rapid, safe technique depends on instant, certain recognition of these tissues. The learner must also understand the method of resecting masses of tissue. Every operator does not use the same technique but the principles must be understood Textbooks and diagrams are of great value for this

purpose Gershom Thompson (1933) and Emmett (1943) have described punch resection very clearly and excellent accounts of loop resection are given by Reed Nesbit (1951) and Barnes (1943) The writer has attempted to demonstrate the punch operation by an animated diagram film. Finally the operator must acquire proficiency in using the instrument In the patient s interests this must be a long process requiring careful supervision. The writer has devised a model (Chapman 1953) which affords practice in the technique of punch resection in conditions which approximate closely to those of the actual operation The bladder and prostatic capsule are represented in rubber (Fig. 31) The hypertrophied prostatic tissue is represented by a plastic substance called Vina mould The upper part of the bladder is not represented and its place is taken by a Perspex window through which the procedure can be observed. When the resection has been completed the resected Vinamould is melted and readily reformed into " prostatic lobes." Using this model it is possible for an experienced urologist to demonstrate technique or to advise a learner while he is making his early efforts. It is also of value for the learner to pause in his resection from time to time and to come to the opposite end of the model and see clearly what has been resected and what he has failed to resect.

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CHAPTER 7

PROSTATIC CANCER

by

J D FERGUSSON

RECENT important discoveries have led to new methods of diagnosis and to striking changes in the management of prostatic cancer The success of hormonal therapy in particular has brought about a new conception of malignant disease and has focused particular attention on the prostate where, so far the response has been studied to best advantage. Meanwhile statistical and histological studies have confirmed the high incidence of prostatic malignancy and have suggested an even wider variation of growth activity than was formerly supposed, for which at present there is no accurate method of biological assessment

Incidence of Prostatic Cancer

Mortality statistics both in England and Wales and in the United States, indicate a moderate though roughly comparable rise during the decade 1941–50 This may in part be accounted for by improved diagnosis but is mainly due to increasing longevity Present indications are that the rise is unlikely to be sustained, despite predictions to the contrary based on earlier figures (Gordon 1941)

Crude Death Rates from Cancer of the Prostate per Million (Males all ages)

	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950
England and Wales	127	142	146	135	145	139	143	137	144	146
United States (Whites) †	145	135	135	141	150	159	160	166	152	153

Registrar General's Statistics for England and Wales.
† Vital Statistics of United States.

Further indication of the importance of prostatic cancer at the present time is afforded by the standardised death rate statistics relating to various primary sites of malignant disease (Hewitt and Brooksbank, 1952) From these it would appear that, in males over the age of thirty five, malignant disease of the prostate is more common than the combined incidence of cancer throughout the remainder of the uro-genital tract The prostate, in fact, is the second commonest site for primary cancer among males in the United States and occupies fifth place in order of frequency in England and Wales. Available figures suggest that the disease is at least as common in negroes as among the white races, but records are insufficient to allow a reliable estimate for Asiatics The supposition that prostatic cancer is rare among Hebrews (Ravich and Ravich, 1951) has not been confirmed by a recent investigation in this country (Gibson, 1954) nor has any linkage with specific blood groups been established.

The above figures relate only to the incidence of overt clinical forms of the disease. Histological research in recent years, however has supplemented the previous studies by Moore (1935) and Rich (1935) and fully confirms the presence of small occult foci of prostatic malignancy in a high proportion of elderly males (Baron and Angrist, 1941 Franks, 1954). These findings suggest that prostatic cancer exhibits considerable variation in its activity for which due allowance must be made in evaluating the response to any specific method of treatment.

Pathology

Contrary to previous views the posterior lobe " of the prostate can no longer be regarded as the seat of election for malignant change. Precise histological studies indicate that the primary growth *(often multifocal) commonly originates in the periphery of the lateral* masses of the gland (Fig 32) often adjacent to though rarely within, an adenomatous nodule (Vernet, 1944 Hirst and Bergman 1954). It is scarcely surprising, therefore, that cancer should sometimes evince itself in the residual prostatic tissue after previous enucleation prostatectomy for benign hypertrophy (Smith and Woodruff, 1950).

Local spread of the primary growth to the region of the seminal

vesicles and lower end of the ureter has been emphasised by Vernet (1944), while involvement of the external urinary sphincter and of the perirectal tissues is less rare than formerly supposed Metastatic spread of the tumour takes place both by the lymphatics and the blood stream. The role of the perineural lymphatics has been stressed by Kahler (1939), but it is doubtful whether the frequency of



FIG. 32. Transverse section of prostate showing area of carcinoma arising in the peripheral zone of the lateral mass of the gland.

secondary deposits in the pelvis and vertebræ can be ascribed solely to this route of dissemination. A more likely channel would appear to be the connection between the peri-prostatic venous plexus and the vertebral veins, demonstrated in a series of injection experiments by Batson (1940) and recently confirmed by Franks (1953*a*) (*Fig.* 33)

Diagnosis

Clinical methods of diagnosis may nowadays be supplemented by recourse to radiology serological examination, and examination of

material obtained from the primary or metastatic sites. Each of these ancillary methods has undergone elaboration in recent years and merits further consideration.



FIG. 33 The results of barium injection of the prostatic veins showing free anastomosis with the vertebral veins (Reproduced from Franks L.M 1954 *J Path. Bact.*, 66, 91 by kind permission of the author and publishers)

(*a*) **Radiological diagnosis** is concerned mainly with the demonstration of bone metastases which are frequently osteosclerotic in appearance and, in the early stages, show a predilection for sites adjacent to the primary growth Evidence of skeletal deposits is

present in approximately 50 per cent of patients at the time of diagnosis The actual proportion may in fact be higher since it is probable, from a study of anæmia in other forms of malignant disease, that widespread bone secondaries are often present without exciting a visible reaction (Shackman and Harrison 1948)

With regard to the prostate itself no method is yet available for direct radio-diagnosis of the primary growth. The demonstration of prostatic calculi does not exclude the presence of cancer and in fact the two conditions often coexist (Cristol and Emmett 1944 Finkle, 1954) Various techniques have been advocated to determine the extent of an established primary growth with the object of assessing its operability or response to treatment. Among these may be mentioned vesiculography prostatic plexus venography and measurement of the size of the prostate with a balloon catheter marking the bladder neck (Chute and Willetts, 1942) Such methods have a limited application and none is in routine diagnostic use.

(*b*) **Serological Diagnosis.** One of the greatest advances in the laboratory diagnosis of malignant disease relates to the discovery that the quantity of acid phosphatase in the serum is often raised in prostatic cancer This enzyme, which was first detected in the prostate by Kutscher and Wolbergs (1935) is only elaborated in quantity by the mature glandular epithelium (Gutman and Gutman, 1938). With the exception of certain anaplastic growths it is generally abundant in malignant prostatic tissue (Gutman Sproule and Gutman 1936) The inference may be drawn that the tumour cells resemble those of differentiated prostatic epithelium, at least in so far as acid phosphatase production is concerned This function has been confirmed by a histo-chemical staining technique (Gomori 1941) It is not surprising, therefore, since enzyme production in the tissues is reflected quantitatively in the serum, that estimations of the serum acid phosphatase frequently show a raised value in patients with prostatic cancer This is particularly evident where metastases are present, significantly high readings being obtained in approximately 80 per cent of cases (Huggins and Hodges, 1941 Sullivan Gutman and Gutman 1942 Herger and Sauer 1945 Herbert, 1946) Where no radiographic evidence of bone secondaries is present the proportion falls to about 30 per cent.

Estimation of the serum acid phosphatase is carried out by the King and Armstrong procedure (1934) the normal range being between 0–3 units depending on the period of hydrolysis. Raised values are occasionally met in conditions other than prostatic cancer and certain modifications of the test are necessary to allow for the quantity of enzyme produced from extra prostatic sources (King and Delory 1948) Of these, the formalin inactivation method of Abul Fadl and King (1947) is effective in eliminating non prostatic phosphatase and has a more positive application than Herbert's alcohol procedure, in which the prostatic enzyme is estimated indirectly Increased quantities of prostatic acid phosphatase in the serum may occur after palpation of a non malignant prostate, but are rarely sustained for more than twenty four hours (Daniel and Van Zyl, 1952)

Recent work on the stability of acid phosphatase in blood and serum samples has suggested that little deterioration takes place over a period of several days if the material is kept at a low temperature. Alternatively the plasma level in blood kept fluid by acid citrate dextrose solutions is maintained more constantly than in separated serum when stored at room temperature (Daniel 1954)

(*c*) **Histological and Cytological Diagnosis.** The microscopical examination of material obtained from either primary or metastatic sites has become increasingly important in recent years, not merely as a means of diagnosis but in providing an objective record of the malignant process before and during treatment (Fergusson and Pagel 1945) Suitable tissue may be obtained by perurethral prostatic resection or by open approach or needle biopsy through the perineum. Recently trans-rectal biopsy has been advocated in cases where the urethral calibre is reduced (Grabstald and Elliott, 1953) Only positive findings are of value and success depends on the size and accessibility of the tumour A comparison of the results obtained by perurethral resection and perineal needle biopsy has been given by Semple (1951) In the case of metastatic deposits material may be secured by direct biopsy of skin nodules and superficial lymphatic nodes, or by sternal puncture and needle biopsy in the case of skeletal secondaries

In addition to routine histological examination fresh tissue may

be subjected to acid phosphatase estimation by staining methods or by quantitative assay Owing to marked differences in the amount of enzyme elaborated by prostatic tissue and the fact that phosphatase is occasionally produced in metastatic deposits from other primary sites, these supplementary methods have a restricted value in diagnosis.



FIG. 34. Smear of the prostatic secretion, expressed per urethram after rectal massage of the gland showing isolated clump of malignant cells.

In recent years the vogue for cytological diagnosis has led to the examination of the prostatic secretion expressed per urethram after rectal massage of the gland (Fig. 34). Opinions differ at present as to the reliability of the method which is, no doubt, largely dependent on the experience of the cytologist. Close correspondence between the detection of malignant cells and the results of subsequent histological examination has been shown by Peters (1952) and this is confirmed in a personal series of over a hundred cases of prostatic disease recently reviewed (Fergusson and Gibson 1955) It seems

prudent to add that a positive cytological report is unusual in the absence of clinical evidence of malignancy and the method must thus be regarded as mainly confirmatory in value. It may however obviate the need for instrumental biopsy

TREATMENT OF PROSTATIC CANCER

Striking changes in the management of prostatic cancer have taken place in recent years particularly in the field of hormonal therapy The response of malignant prostatic tissue to alterations of the sex hormone balance (Huggins and Hodges, 1941) suggested a new concept of hormone dependent tumours whose activity might well prove subject to endocrine control. Contemporaneously the synthesis of an orally active oestrogenic substance, stilboestrol (Dodds *et al.*, 1938) provided an immediate opportunity for testing this hypothesis The success of hormonal therapy has since been universally acclaimed but with wider experience certain limitations as to its effectiveness have become apparent. In no instance has the complete disappearance of a growth been recorded. On this account there has been a tendency in certain quarters to devise new methods of irradiation therapy and to revive interest in the field of radical surgery At the present time therefore, the active treatment of prostatic cancer affords a number of alternatives—each adaptable to certain phases of the disease, and, in many instances supplementary to one another

Surgery

(*a*) **Radical surgery** at present remains the only treatment offering a prospect of complete cure. The proportion of suitable cases will depend on the circumstances of diagnosis and on the criteria of operability imposed by individual surgeons. In health-conscious communities where routine examinations are frequently performed, the opportunities for the detection of operable growths by rectal palpation are correspondingly increased. When, however investigation is only undertaken after the onset of positive urinary symptoms the chances are reduced, and in most cases the malignant process is found already to have extended beyond the operative field. These

considerations, in part account for the disparity between the operability rates reported from certain clinics in the United States and Great Britain respectively In the former where the continued advocacy of perineal surgery has provided a stimulus to discriminative rectal examination a rate of between 10 and 15 per cent is not unusual, while higher figures are recorded by Kimborough and Rowe (1951) Against this the proportion of operable cases in Great Britain amounts to less than 5 per cent mainly owing to patients failing to attend for examination until symptoms are well established

A decision whether or not to operate will be further influenced by the knowledge that apparently localised primary growths are not infrequently associated with concealed metastases Despite this, however Jewett (1948) has adduced cogent statistical reasons in favour of radical surgery in a series of early cases treated at the Johns Hopkins Hospital On the other hand mere histological confirmation of malignancy during a preliminary biopsy does not necessarily constitute sufficient evidence on which to proceed to the radical operation. The high post mortem incidence of occult prostatic cancer suggests that some growths pursue a relatively benign course and, if such tumours could be distinguished, there would seem little grounds for subjecting the patient to the risks and possible complications of extended surgery In the absence of any criteria of growth activity there has recently been a tendency in certain centres to disregard this conception and to accept eradication as the logical procedure for all discrete primary growths (Hudson *et al.*, 1954) It would seem, however that the treatment of asymptomatic prostatic cancer should be tempered by an understanding that in certain circumstances it may be wiser to allow the patient to remain in symbiosis with his tumour

A similar problem may arise in cases where, under the influence of hormonal therapy a previously inoperable prostatic growth has regressed to a point within the technical limits of operability Taking the view that the tumour response is transitory in nature and thus unlikely to exceed the life expectancy Scott (1953) has advocated the performance of radical prostatectomy The number of cases under these conditions in which the presence of metastases can

confidently be excluded must be small and, unless this proviso obtains, palliative perurethral resection would appear likely to offer equal benefit with less risk. Having regard to these qualifications the applicability of radical prostatectomy, at any rate in this country must be considered limited, and this view is endorsed by most British Urologists

In those cases deemed suitable for radical surgery a choice of procedure is available. While various modifications of the perineal route are often preferred in the United States and on the Continent (as affording the best opportunity for preliminary biopsy), the retropubic approach (Millin 1947) and the transvesical method put forward by Hey (1945) have found some favour in Great Britain. Opinions differ as to the importance of supplementing radical prostatectomy by castration or hormonal therapy In all cases, however save where subsequent microscopy confirms the complete removal of a small discrete tumour this course would seem obligatory

(*b*) **Palliative surgery** is indicated for the relief of urinary symptoms when radical treatment is precluded by metastasis or local extension of the primary growth and when adequate improvement cannot be effected by hormonal therapy Save in advanced cases of urinary obstruction perurethral resection is preferable to cystotomy drainage, and affords a method, which may be repeated if necessary without incurring the disadvantage of a suprapubic fistula. In all cases it can, and should be, supplemented by oestrogen therapy or castration. Examination of the prostatic tissue removed at subsequent resections in the same patient during hormonal therapy may give information concerning the response to treatment and, hence, the prognosis (Fergusson and Franks, 1953)

(*c*) **Castration and adrenalectomy** although palliative surgical procedures, are dealt with in a subsequent section relating to hormonal control, and in Chapter 13 "Adrenal Surgery"

Hormone Control Therapy

This is based on the assumption that prostatic malignant tissue is, in general, composed of cells resembling those forming the epithelium of the mature gland in their dependence upon hormones. Animal experimental work by Huggins and Clark (1940) showed that

involutionary changes could be induced in cystic hyperplasia of the dogs prostate by castration or œstrogen administration Application of the same principles to advanced cases of human metastasising prostatic cancer resulted in a similar inhibitory effect while conversely androgens activated the tumour (Huggins and Hodges 1941). Corresponding regression of the malignant process after œstrogen administration was recorded independently by Herbst (1942a) and to a lesser extent, after irradiation of the prostate and testes by Munger (1941). Since then evidence has accumulated to show that a majority of prostatic growths are at any rate temporarily sensitive to alterations in the hormonal milieu. This evidence is based on signs of clinical improvement following œstrogen administration and other forms of endocrine therapy together with changes in the radiological appearance of bone metastases, reduction of the serum acid phosphatase content, and alteration in the histological features of the tumour A small number of anaplastic growths (probably less than 10 per cent, however remain unresponsive to hormone therapy

The success of hormone control therapy depends on reducing the potential stimulating effect of androgens on the malignant prostatic tissue. This can be achieved most simply either by removal of the major source of androgens (castration) or by increasing the amount of circulating female hormone (œstrogen therapy) It is probable that the latter does not exert a direct neutralising effect, but acts by depressing the output of pituitary gonadotrophin thus leading to a decrease in androgen production by the testes and adrenals. Despite this indirect mode of action the therapeutic response is similar save for the incidence of certain side effects due to direct œstrogen stimulation. The initial choice of treatment in practice, therefore, lies between removal of the testes (in which case a limited production of androgens may continue from the adrenals) or giving œstrogens with a view to diminishing, in general, the activity of all sources of androgen production Adoption of the latter alternative presupposes an ability on the part of the patient to submit to sustained treatment.

The results in a large collective series of cases (Nesbit and Plumb 1946) indicate that castration is slightly superior to œstrogen therapy but that, in metastasising cancer a combination of the two is more

effective than either method used independently On the other hand, castration implies an unpalatable, if trivial, operative procedure, and recent experience indicates that high oestrogen dosage can produce an equally beneficial effect No matter whether either or both methods are employed the tumour response is almost immediate, and recognisable histological changes can be demonstrated within a period of forty-eight hours (Fergusson and Franks, 1953) Unfortunately, after a varying period, often between twelve and eighteen months a proportion of growths show signs of reactivation, presumably due to a compensatory increase in androgen production by the adrenals. This not infrequent resurgence of activity raises further problems in management firstly with regard to the timing of the initial treatment so as to obtain the maximum symptomatic benefit and secondly, with reference to the effectiveness of increasing the oestrogen dosage or performing alternative operative procedures in an attempt to secure a further response.

Opinions differ as to whether hormonal therapy should be universally instituted at the time of diagnosis of prostatic cancer or whether on account of the possibility of a transient response, such treatment should be reserved until symptoms become troublesome. As, however the nature and duration of the response at present remain unpredictable, and since the activity of the untreated growth cannot be accurately assessed, deferment can only be justified on speculative grounds With regard to securing a further response from tumours showing signs of reactivation an increase of oestrogen dosage may prove effective in a certain proportion of cases (Fergusson and Franks, 1953) In the remainder various procedures have been put forward with a view to removing extra-gonadal sources of androgen (bilateral adrenalectomy), or curtailing the production of stimulating gonadotrophins from the pituitary (hypophysectomy or pituitary irradiation) Present indications are that, while in some cases so treated the response is dramatic and can be substantiated by histological evidence of tumour regression the period of relief remains uncertain In summary the effects of hormonal therapy have been encouraging in so far that despite no actual record of cure, a measure of control over the neoplastic process has in many instances been achieved for prolonged periods The mode of action,

however is quite different from that of radiotherapy and other procedures and hence the method must be regarded as ancillary rather than exclusive

Certain practical aspects of hormonal therapy will now be considered

Castration. Most surgeons nowadays advocate *subcapsular* orchidectomy which may be conveniently performed through a scrotal incision exposing both testes On incising the tunica albuginea the contained testicular tissue is separated by blunt dissection and removed after ligation and division of the rete testes There is no need for the introduction of a prosthesis since after suture of the tunica, the residual cavity becomes partially filled with organising clot which reproduces, in miniature, the normal contours Subsequent histological examination of organs thus treated has shown no recurrent growth of testicular tissue. Castration may be supplemented by œstrogen therapy but conversely is seldom of additional benefit in patients previously responsive to œstrogens In these, the testes are usually found to be small (physiological castration) and orchidectomy is unlikely to produce more than temporary psychological benefit.

Œstrogen therapy is based on the premise that circulating œstrogenic compounds inhibit the production of androgens and thus modify the activity of androgen-dependent prostatic malignant tissue. This effect is probably brought about by the suppression of pituitary gonadotrophic activity rather than by a direct effect on the testes. The possibility of a supplementary œstrogen effect on the tumour tissue itself cannot at present, be excluded

Until comparatively recently the only available œstrogenic substances were those extracted from animal sources, either in natural form or modified by chemical substitution to produce an enhanced physiological response. The synthesis of stilbœstrol (Dodds *et al* 1938) provided a compound of much greater potency and one, moreover which was highly active on oral administration This important discovery came at an opportune time since it was possible, in the light of Huggins work, to apply it to the treatment of prostatic cancer From the results achieved it may now be said that this represented the first occasion on which any form of cancer had been

favourably affected by oral therapy In addition to stilboestrol similar oestrogenic compounds have since been synthesised, of which hexoestrol and dienoestrol are in frequent therapeutic use. These synthetic oestrogens form a group unrelated in chemical constitution to the naturally occurring hormones, and differ also in their high degree of potency when given by mouth. For the latter reason they are thus preferred in the treatment of prostatic cancer unless contra-indicated by gastric intolerance.

General opinion favours the use of stilboestrol, though in some instances dienoestrol appears to be better tolerated. No unanimity has yet been reached on the optimum dosage, but recent histological studies, in correlation with the clinical response, have indicated that larger amounts should be given than are usually prescribed (Fergusson and Franks, 1953) In view of this and from a review of the survival periods of patients who have received various dosages, it is recommended that at least 100 mgm. a day should be taken and that no reduction to a lesser maintenance dose be made subsequently There is no evidence that intolerance is any more frequent after these larger doses than when small amounts are prescribed. Absorption of stilboestrol from the alimentary tract is diminished by the ingestion of mineral oil (Hsiung *et al* 1948) and medication with paraffin emulsion is thus best avoided during treatment. In the few cases where oral administration is accompanied by troublesome nausea castration is generally advisable. If additional hormone therapy is then required recourse may be had to the subcutaneous implantation of oestrogen pellets These are available in the form of 100 mgm. compressed tablets of stilboestrol, the absorption rate of which has been calculated at about 1 mgm. a day (Bishop and Folley 1951). The effect on the malignant process is, therefore, probably too small to warrant the use of this method except as a supplementary measure.

Side Effects of Hormonal Therapy

Although the results of oestrogen therapy and castration are more or less identical as far as retardation of the prostatic growth is concerned, their mode of action, as already mentioned, is dissimilar Apart from decreasing the output of pituitary gonadotrophin

stilbœstrol administration leads to a general increase in the amount of circulating œstrogen. In consequence certain side effects may be induced affecting the urogenital system and accessory reproductive organs or connected with disturbance of metabolism In the former case shrinkage and retraction of the testes, with a corresponding decrease of libido are frequently observed, while histological changes in the form of squamous metaplasia of the posterior urethra (Wattenberg and Rose, 1945) and of the prostate itself (Nanson 1950) have been recorded Hypertrophy of the breasts with tender ness and occasional pigmentation of the nipples is almost the rule and this, though not always sustained during treatment, gives some indication of an effective œstrogen intake. A few cases are recorded in which a cancer of the breast has developed during œstrogen therapy but Campbell and Cummins (1951) suggest that in most instances this has been metastatic rather than primary It seems possible that the mammary activity induced by œstrogen therapy may favour the survival of malignant emboli Skin pigmentation is often seen most frequently affecting scar tissue, the midline of the lower abdomen and the ano-scrotal raphe.

Synthetic œstrogens are stated to be metabolised by the liver with greater difficulty than the naturally occurring hormones (Herbst, 1947) and a few cases of hepatitis have been recorded during treatment (Stirling, 1945 Wattenberg, 1946) The incidence of serious complications, however is small and becomes insignificant in comparison with the beneficial response obtained in a majority of patients undergoing treatment

Adrenalectomy

See also Chapter 13 " Adrenal Surgery

It is now widely recognised that a proportion of prostatic growths which show a satisfactory initial response to œstrogen therapy or castration subsequently display evidence of reactivation. Some no doubt become altogether independent of hormone control while others are thought to be influenced by increased androgen produc tion from extragenital sources Enlargement of the adrenals was noted at autopsy in a number of reactivated cases by Herbst (1942) and it is now concluded that these glands represent the main residual

androgen depot. Acting on this assumption bilateral adrenalectomy was first performed by Huggins and Scott (1945) and Cox (1947), *but the results although temporarily encouraging, were unsatisfac*tory owing to inadequate replacement therapy. Nowadays, however the availability of cortisone renders such treatment both safe and practicable. Considerable discrimination is called for in the selection of cases for operation and the following criteria have been advanced by Huggins (1952, personal communication). In the first place there should be positive evidence of a previous response to œstrogens or castration and, secondly clear indications of increasing metastatic activity despite continued hormonal therapy.

The operative technique of adrenalectomy presents but little difficulty to those experienced with the exposure of the kidney through the bed of the eleventh or twelfth rib (p. 242). The success of the operation however depends mainly on the effective conduct of the pre- and post-operative regime, details of which have been furnished by Huggins and Bergenstal (1951). Recent work on the absorption of cortisone by the oral and intramuscular routes respectively has suggested the following modification (Fergusson, 1954) whereby a suitable reserve of this substance may be built up before operation. It has also been found that the routine subcutaneous implantation of 200 mgm. DOCA at operation is effective in maintaining salt and water balance.

Steroid Cover for Total Adrenal Removal

Two days before operation
200 mgm. Cortisone acetate in divided doses intramuscularly Oral salt 4 c.c.
One day before operation
200 mgm. Cortisone acetate in divided doses intramuscularly Oral salt 4 c.c. + 5 mgm. DOCA intramuscularly
Day of operation
100 mgm. Cortisone acetate early morning (orally). 200 mgm. DOCA implanted in subcutaneous fat of wound (at operation).
50 mgm. Cortisone acetate intramuscularly at 12 noon and then six-hourly
Op. + 1 day Cortisone acetate 50 mgm. intramuscularly six-hourly
Op. + 2 days Cortisone acetate 50 mgm. intramuscularly eight-hourly
Op. + 3 days Cortisone acetate 50 mgm. orally eight-hourly
Op. + 4 days Cortisone acetate 25 mgm. orally 6 a.m., 11 a.m., 4 p.m., 10 p.m.
Op. + 5 days Cortisone acetate 25 mgm. orally 6 a.m., 2 p.m., 10 p.m.

Op + 6 and subsequent days Cortisone acetate 25 mgm. twelve-hourly

Give 2-3 litres of fluid per day supplemented by blood L. norepinephrine glucose and salt as required

Estimate daily (during the post-operative period) the early morning serum concentration of sodium and potassium, and the fasting blood-sugar

Observe fluid intake and output, and supplement if possible by daily check weighing to avoid danger of water retention.

Continued substitution therapy with cortisone is required in all cases, a majority of patients being maintained indefinitely on approximately 50 mgm daily Reimplantation of DOCA 200 mgm. is desirable at intervals of approximately six months Despite these measures the adrenalectomised patient remains exposed in the event of metabolic disturbances induced by other causes, to the risk of Addisonian attacks which may demand supplementary treatment for their relief Resistance to bacterial invasion is also reduced and intercurrent infections may necessitate modifications of the replacement therapy

Hypophysectomy and Irradiation of the Pituitary

Suppression of pituitary activity and hence a curtailment of the production of gonadotrophic hormones, may be brought about either by hypophysectomy or irradiation of the gland. In skilled hands the former may be accomplished with low operative mortality and symptomatic improvement is often immediately evident (Olivecrona, 1955). The alternative procedure, which appears capable of inducing similar relief embodies the introduction of radon seeds (Forrest and Peebles Brown 1955) or radio-active gold grains or yttrium rods into the hypophysis by the trans-sphenoidal route (Fig. 35*a* and 35*b*) This is accomplished under radiographic control and can be greatly aided by the employment of an X-ray image intensifier which permits prolonged screening during the passage of the needle introducer

Both operative and irradiation methods suffer the disadvantage that destruction of the pituitary may not be absolute, and various tests are available to indicate the subsequent complications or otherwise of functional arrest (Luft and Olivecrona, 1953) Elimination

of functional activity necessitates substitution therapy with cortisone, though in considerably smaller doses than those required after adrenalectomy

It is difficult at the present time to gauge what position adrenal-



FIG 35 (a). Method of implantation of radio-active material into the pituitary gland by the trans-nasal route. A needle-introducer has been passed through the sphenoidal sinus into the pituitary fossa.

ectomy and pituitary destruction will ultimately occupy in the treatment of advanced prostatic cancer The main problems affecting their expediency appear to be

(a) The inability to distinguish between tumours which are hormone dependent and those which have become dissociated from endocrine control

(*b*) The fact that patients suitable for operation on theoretical grounds may be surgically unfit for other reasons

(*c*) The chance of metabolic disturbance during the post-operative period and the need for permanent substitution therapy



FIG. 35 (*b*). Radio-active yttrium rods implanted into the substance of the pituitary

(*d*) The possibility that the post-operative response of the tumour and consequent relief of symptoms may be no more permanent than that following other methods of androgen control

The Response to Hormonal Therapy

The response to hormonal therapy may be subjectively or objectively assessed according to alterations in the clinical symptoms and

signs More tangible evidence, however can be adduced from periodic repetition of the specific investigations used initially to confirm the diagnosis.

The Response to Castration and Œstrogen Therapy

A voluminous literature has accumulated during recent years from which only a brief abstract can be given here. (The response to adrenalectomy is considered in a succeeding section.)

Clinical Response. In general about 80 per cent of cases show initial improvement, which is sustained in 50 per cent for over a year In these the primary growth tends to diminish in size and to lose its malignant characteristics with accompanying relief of the associated urinary symptoms In addition to improved evacuation of the bladder a few cases are recorded in which obstruction of the upper urinary tract due to infiltration of the primary growth around the lower ends of the ureters, has been relieved. On the other hand, when the growth has advanced distally and has invaded the external urinary sphincter shrinkage, following œstrogen administration, may sometimes lead to incontinence (Rose, 1944)

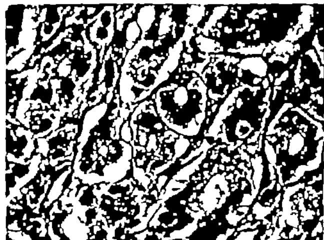
At the same time objective evidence of growth regression may be afforded by the disappearance of affected superficial lymph nodes (Herger and Sauer 1945 Fergusson and Pagel, 1945), and of secondary cutaneous nodules (Huggins 1948) Coincident reduction of œdema, where this has been due to lymphatic obstruction may also take place. Recovery from paraplegia, presumed due to spinal metastases, has been recorded by several authors (Clark and Viets, 1943 Nesbit and Cummings, 1944 Alyea, 1945) and has been observed on three occasions in a personal series. General evidence of improvement in the form of loss of metastatic pain gain in weight, recovery from anæmia, and reduction of the sedimentation rate (Boylan and Tillisch 1948) have been the general experience of many observers.

Radiographic Response. Convincing signs of the regression of bone metastases have been noted on numerous occasions (Nesbit, Pazzus and Cummings, 1944 Huggins, 1946) On the other hand, alterations in the radiographic appearance are capable of misconstruction and may depend on changes of technique, so that evidence

in this respect adduced by other observers has not always been above criticism. Regression of pulmonary and mediastinal lymph node metastases may be more convincing (Alyea and Henderson 1942 Alyea, 1945)

Serological Response Reduction of the serum acid phosphatase content during treatment has been described by Huggins and Hodges (1941) and by numerous other workers (Watkinson *et al.*, 1944 etc.) Herbert (1946) stated In patients showing a high serum phosphatase initially the fall under treatment is the earliest objective sign that the tumours are sensitive to œstrogens The simultaneous behaviour of the serum alkaline phosphatase in cases with bone metastasis has been investigated by Dean Woodward and Twombly (1944) an initial rise being generally succeeded by diminishing values. In cases showing subsequent reactivation at the metastatic sites both acid and alkaline phosphatase levels usually increase, the latter often providing the first indication of renewed activity

Histological Response. Histological changes in the tumour during treatment provide the most satisfactory evidence of the effect of hormonal therapy (Fig. 36) Repeated biopsy studies have shown both qualitative and quantitative responses on the part of the malignant tissue (Schenken Burns and Kalhe, 1942 Heckel and Kretschmer 1942 Fergusson and Pagel 1945) In addition to major structural changes a reduction in the average diameter of the tumour cell nuclei has been observed together with an impaired capacity of the malignant cells to elaborate phosphatase. The latter observation has been found also to apply to metastatic deposits (Fergusson, 1946) Close correlation between the histological changes and the symptomatic course of the disease has been shown in a series of thirty-three cases in which repeated biopsy examination was possible (Fergusson and Franks, 1953) One of the most remarkable features arising from a serial study of malignant prostatic tissue during hormonal therapy is connected with the subsequent reactivation of the tumour Histological evidence suggests that in this circumstance, the primary growth often remains suppressed despite renewed and widespread activity on the part of the metastases (Huggins, 1942 Gilbert and Margolis 1943 Fergusson 1946)



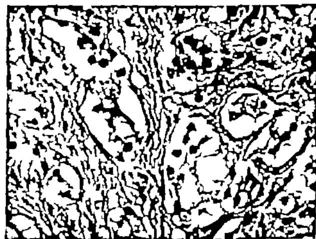




FIG. 36. Three biopsy studies of malignant tissue from the same prostate before and, at intervals of ten days and seventeen months respectively during oestrogen therapy (Reproduced from Fergusson, J. D., and Franks, L. M., 1953 *Brit J Surg* 40, 422, by kind permission of the publishers.)

The Survival Period The survival period of cases receiving hormonal therapy has been found on average to be significantly prolonged (Nesbit and Plumb 1946 Fergusson 1948) As might be expected cases without obvious evidence of metastasis when first seen carry a better prognosis. No critical analysis is yet available regarding the relationship between the initial serum acid phosphatase level and the survival period, but histological grading of the tumour where practicable, has proved of little value in establishing the outlook (Fergusson and Franks, 1953).

Response to Bilateral Adrenalectomy

The response of reactivated prostatic cancer to total adrenalectomy must be interpreted with caution on account of the risk of confusion with the changes induced by previous hormonal therapy (or castration) or alternatively with the effects of cortisone substitution. In practice, the interval between castration and subsequent adrenalectomy is generally sufficiently long to permit a separate assessment of the results of both procedures The administration of cortisone by itself may bring about some symptomatic improvement (Taylor Ayer and Morris, 1950 Hayward 1953) which it may be difficult, temporarily to distinguish from the effect of adrenalectomy It is not considered, however that cortisone significantly modifies the course of the malignant process (Huggins and Bergenstal, 1951), and further evidence that any tumour response is due to adrenalectomy rather than the replacement therapy is afforded by a recent study of calcium excretion in patients with metastasising breast cancer (Fergusson, 1954). In these cases the osteolytic activity of bone deposits was shown to decrease after removal of one adrenal before any substitution therapy had been commenced

Sufficient information is now available to show that in a proportion of reactivated cases of prostatic cancer submitted to adrenalectomy a further measure of growth control can be obtained comparable to that previously resulting from other methods of hormonal therapy (Fergusson 1954) Evidence of the clinical response is shown by a marked shrinkage of the primary growth and by the cessation or relief of metastatic pain Even more striking is an improvement in the general condition allowing the return to ambu

lant activity of patients previously bedridden Changes in the radiographic appearances of osteosclerotic bone deposits, however is seldom as manifest as in the case of osteolytic metastases in mammary cancer treated by the same method. Following adrenalectomy a

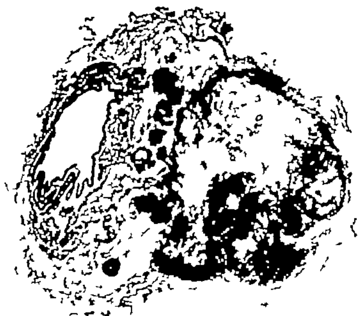


FIG 37 Section through the prostate and rectum from a case of cancer of the prostate dying six weeks after bilateral adrenalectomy Note area of massive necrosis in the growth. Similar necrosis was observed at a number of metastatic sites. (Reproduced from Franks, L. M., 1953 *Brit med. J* ii, 359 by kind permission of the author and publishers.)

decline in the serum acid phosphatase value frequently occurs (Huggins and Bergenstal, 1952 Scardino, Prince and McGoldrick, 1953 Butler *et al* 1953) which, in combination with symptomatic improvement, may be construed as an indication of the tumour response. Extensive histological changes in both primary and secondary growths have been described by Franks (1953b) in a case dying six weeks after operation (Fig. 37).

Response to Hypophysectomy and Pituitary Irradiation

These procedures must be regarded as still in an experimental stage and little objective evidence of tumour response has so far been recorded in cases of prostatic cancer Reports of symptomatic improvement, however are sufficient both in degree and duration to justify continuance in selected cases, and the more tangible results achieved by such treatment in mammary cancer serve to reinforce this view

Radiotherapy

The present position of radiotherapy in the treatment of prostatic cancer is hard to assess Prior to the introduction of hormonal therapy it was widely accepted that irradiation had a limited value in controlling the activity of the primary tumour and prolonging the period of survival. The initial results of œstrogen therapy and castration, however led to its almost universal discontinuance, but interest in the method has recently been revived This has been due partly to the prevalence of tumours which have become resistant to hormonal control and partly to the availability of radioactive isotopes in a form suitable for therapeutic application The inoculation of radioactive colloidal gold into the prostate has been shown by Flocks (1952, 1953) to give a satisfactory measure of control over the primary tumour and appears applicable in cases with local extension provided that surgical access is feasible. Rapid transference of the radioactive material to the liver and elsewhere may however take place, and the period of full radioactivity at the primary site is, therefore, inconstant Since there is no selective affinity for colloidal gold at the sites of metastasis the method is only suitable for the treatment of the primary growth Little advance has been made in the employment of radiotherapy for metastatic lesions beyond the suggestion that injections of radioactive gallium might be of value in the treatment of skeletal secondaries (Lang, 1951 Herbst 1952) This substance is of low toxicity and has been found, from animal experiments, to become localised in the bones in a concentration ten times as great as in other body tissues. Recent observations, however have shown that it is deposited mainly in areas of active osteogenesis peripheral to the site of metastasis and

is thus probably unable to exert any significant therapeutic effect on the tumour tissue In general it may be said that insufficient time has yet elapsed following the introduction of treatment with radioactive isotope to form a clear opinion as to their value.

The main drawback to the effective use of radiotherapy continues to lie in the relative insensitivity of most prostatic tumours. Thus the delivery of an adequate dose to inactivate the growth is inevitably fraught with the risk of damage to the surrounding normal tissues.

In describing the developments which have taken place in the study of prostatic cancer during recent years emphasis has been laid on those directly concerned with the diagnosis and treatment of the disease. It is inevitable, in so doing, that much laboratory research, particularly that concerned with enzyme studies, biochemistry of steroid hormones and tumour transplantation should escape full recognition At the same time, being solely concerned with recent developments, it is not intended that a comprehensive picture of the management of the disease should be presented. Prostatic cancer as an entity remains unchanged, and it is for time and experience to show how far and how properly the advances described may ultimately take their place in influencing its course.

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CHAPTER 8

RENAL TUMOURS

Diagnosis

THE classical triad of "hæmaturia, pain and tumour" remains unaltered and although it may often be due to conditions other than a neoplasm, there is no excuse for omitting a full urological investigation should any or all of the components be present. In spite of this laudable sentiment it is a depressing thought that 28 per cent of renal neoplasms in the *British Association of Urological Surgeons Review* were inoperable when first seen by the urologist (Riches, Griffiths and Thackray 1951)

Once having established the kidney as the source of symptoms, the diagnosis of the actual lesion is usually a simple matter but difficulty can occur in differentiating between neoplastic and cystic conditions, and the use of aortography has been found very valuable in such cases (Griffiths 1950 Riches, Griffiths and Thackray 1951). Neoplasms frequently show areas of "laking" of the opaque medium and if this sign is present it is probably diagnostic of a tumour (see p 54)

However the final proof may only be obtained by exploration, and even if a cyst is found it should be remembered that such a cyst can conceal a carcinoma. This occurred in a partial nephrectomy case of the author's, and has also been recorded by Badenoch (1950), while Prather (1950) concludes that any space-filling lesion in a kidney must be explored

The world's most comprehensive review of renal neoplasms was presented to the British Association of Urological Surgeons by Riches, Griffiths and Thackray in 1951 when 2,314 cases were collected from British urologists and analysed in detail. Some important generalisations can be drawn from this exhaustive review Gravitz type tumours accounted for 75 per cent of the total numbers,

men being affected twice as often as females. Although the classical triad of hæmaturia pain and tumour drew attention to the pathology in most instances, 10 per cent of silent cases were discovered accidentally in the squamous carcinomata and Wilms tumour groups Eleven cases of unsuspected adenocarcinoma were discovered incidentally during routine post mortem examinations Calculi were associated with 29 per cent of the cases of squamous-celled carcinomata of the pelvis, but bore no important relation to other types of growth

It has long been taught that varicocele was an important finding in cases of renal neoplasms, but there is no evidence to support this, and the perpetuation of such a view should be discouraged.

Nearly 50 per cent of the 189 Wilms tumours occurred between the ages of 2 and 4 years and mostly presented with an abdominal mass, hæmaturia being present in only 18 per cent

While all urologists are agreed upon the advisability of tying the pedicle before extensive manipulation takes place, the actual incisions used in this series are instructive. A lumbar incision was used in 940 cases with a 4 per cent operative mortality while only 167 transperitoneal incisions were used, with a mortality of 5 per cent. It is also interesting to note that involvement of the renal vein by growth raised the overall operative mortality from 3 per cent to 13 per cent.

Treatment of Renal and Ureteric Neoplasms

Nephrectomy at the earliest possible moment is still the procedure of choice, but one cannot state too often that hæmaturia must always be fully investigated and full investigation includes adequate radiological definition of the upper urinary tract regardless of what is found in the way of a simple vesical papilloma or a bleeding prostatic adenoma

The survival rates after nephrectomy are approximately 44 per cent after 3 years and 30 per cent after 5 years while these figures are very greatly reduced when the renal vein is involved in growth.

Pelvic tumours require a complete nephro-ureterectomy using two incisions. Even benign papillomata of the renal pelvis produced a

recurrence in the ureteric stump in 8 per cent of cases where simple nephrectomy had been performed

Primary tumours of the ureter are nearly all malignant and should be treated as such by complete nephro-ureterectomy

Combined Surgery and Radiotherapy

Riches and his colleagues found it impossible to judge whether pre-operative irradiation had any useful place in the treatment of adenocarcinoma owing to the small numbers involved, but they think this combination should be considered more seriously particularly in view of the fact that 28 per cent of the cases were already inoperable when first seen Post-operative irradiation resulted in a definite improvement in the survival rates after 1 3- 5- and 10-year intervals and appeared to mitigate the otherwise serious effect of involvement of the renal vein

In the case of Wilms tumours, radiotherapy would appear to be invaluable The recommendation is that small localised tumours should be treated by nephrectomy alone. If there is doubt about the complete removal of all growth post-operative irradiation should be given If the tumour is considered too large to remove, deep therapy will reduce its size and render it operable. Removal should be carried out after about three weeks treatment and before the skin reactions occur It is probable that most urologists in Britain today would advise irradiation following nephrectomy for Wilms tumours.

Secondary Metastases

Metastases from renal adenocarcinomata are sometimes solitary and accessible to surgery although opinions vary about the advisability of removing them or not. McClanahan and Bonann (1953) reported three cases where bone secondaries were the presenting feature of a renal carcinoma, and they emphasise the fact that such deposits may closely resemble a primary bone tumour Single deposits usually affect the long bones and they reported a two-year survival after amputation of a humerus in such a patient.

Further examples of the successful removal of solitary metastases are recorded, while Higham (1953) has reported a case where two years after nephrectomy a lung secondary was removed by lobectomy

followed eighteen months later still by the removal of an encapsulated brain metastasis from the right frontal lobe. The patient was still at work six months later

Surgical Approach to the Kidney

Any recent advances in operative technique have been confined to the surgical approach, in an attempt to secure the pedicle before extensive manipulation is performed. The importance of removing all of the perirenal fat and kidney *en bloc* together with any glands along the pedicle, has been stressed by Beare and McDonald (1949) who found that 343 of 488 hypernephromata removed showed malignant involvement of the capsule. Surgical incisions will always remain a matter of personal choice, while no one incision is suitable for all cases, but perfectly adequate exposure of small tumours can be obtained with an incision through the bed of the twelfth rib and I am not convinced that the abdominal transperitoneal approach makes access to the pedicle any easier in such cases

Donovan (1955) has recently suggested approaching the posterior aspect of the pedicle through the bed of the twelfth rib by displacing the kidney and its fatty coverings forwards into the abdomen, rather than trying to deliver the mass out of the wound before approaching the main vessels. I have no experience of this manœuvre at the present time, but it appears to be a very rational approach

Where the tumour mass is large and lying high up under the diaphragm the thoraco-abdominal route recommended by Mortensen (1948) and by Chute (1949 1951) gives a quite extraordinary exposure, though it is time-consuming and not without morbidity

It should be noted that these incisions are more popular in America where extensive aortic node dissections are carried out, whereas in this country most urologists prefer to use deep X ray therapy in such cases, and are therefore content to remove the kidney and its surrounding fat with as little manipulation as possible

Thoraco-abdominal Incision

Chute and Soutter (1949 1951) recommend this approach to the pedicle for large renal tumours, and consider that it has enabled them to remove some kidneys which would have been inoperable through any other incision

Starting from the outer edge of the rectus muscle at the level of the umbilicus the incision extends upwards and laterally over the eleventh rib which is resected The pleural cavity is entered, and after the phrenic nerve has been crushed, the incision is deepened through the diaphragm and the abdominal muscles, into the peritoneal cavity On the left the spleen and kidney now tend to project into the wound without further manipulation. On the right side the liver is gently retracted upwards.

The renal vessels are easily exposed and divided almost before any mobilisation is performed, after which the kidney is removed under direct vision. When the peritoneum and diaphragm have been closed and the lung fully expanded the pleura is closed without drainage, and the muscle layers approximated in the usual way

Dorso-lumbar Approach to the Kidney and Adrenal with Osteoplastic Flap

This approach was described by Nagamatsu (1950) who claims that it gives excellent exposure of the upper renal pole and adrenal fossa. The lower three ribs are exposed (just medial to their angles) by a vertical incision which then sweeps laterally along the upper border of the twelfth rib Short lengths of the ribs are resected and the complete osteoplastic flap is turned upwards The upper ureter can be approached by making the lower limb of the incision much more oblique, instead of following the line of the twelfth rib It is claimed that the resection of small pieces of rib instead of mere division prevents overriding during convalescence, thereby considerably reducing discomfort.

Nagamatsu emphasises the value of this incision as a planned procedure for specific difficulties. It is not advocated as an expedient to the lumbar incision found inadequate after much time has been lost

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CHAPTER 9

BLADDER TUMOURS

by

D M WALLACE

A REVIEW of the available statistics relating to tumours at various sites in the body will naturally give the impression that cancer at all sites is increasing, partly due to more accurate diagnosis and partly due to there being a greater number of persons at risk in each age group

In order to obviate these possible errors Case (1956) has plotted the age of death of persons born in different decades from different forms of cancer Cancer of the lung is thus shown to be causing death in greater numbers in progressively younger male age groups. Tumours of the bladder i e. carcinoma and papilloma combined, are also behaving in a very similar fashion For each decade of men at risk deaths are occurring from this disease at an increased rate in the younger age groups.

Clemmensen (1956) working with the morbidity returns of the Danish Tumour Registry has been able to show a similar increase, but the Danish figures which are cases recorded while still alive, not death certification suggest that the increase is occurring mainly in one group, the males living in towns.

This selective increase in one group of the population raises the possibility of there being a common extraneous factor such as environmental exposure as would be encountered in industry or a factor of changing social habits, especially diets, smoking, drinking, etc.

The value of an accurate history both of the patient's occupation and of his habits, cannot be exaggerated, since only by examining adequate histories of large numbers of cases retrospectively will it be possible to select possible causative factors

Classification of Tumours

During the last decade the treatment of bladder tumours has tended to swing from radical surgery to either conservative surgery or to radiotherapy Although this change in the approach to the problem has been partially due to the elaboration of new techniques in the field of radiotherapy it is also partly due to the better understanding of the disease process and to the appreciation of the natural history of the disease.

Confusion has been caused by the numerous different methods of presenting results Some series have been classified according to the histological type of tumour without reference to the extent of spread. Other series have been classified according to the extent of spread without reference to the histological type. Few series have included both factors

Assessment of the spread may be a clinical one or it may be a pathological one. It is obvious, however that a pathological staging, although more exact, is only applicable to cases where the tumour has been removed and, therefore results based on this method cannot be compared with results of conservative therapy whether endoscopic, radiotherapeutic or chemical.

It is only by applying a clinical assessment to all tumours and staging each case on the result of the clinical examination as honestly as possible that comparisons can be effected between various methods of treatment.

The pathological staging, that is the extent of spread of a tumour as determined by the examination of an operative specimen, is an essential check on the accuracy of the clinical stage, but as it can only be applied to cases treated surgically it cannot be used for all series. The pathological staging will be more accurate for prognosis but even this will vary with the extensiveness of the operation—one case treated by partial cystectomy only would be less accurately assessed than a similar case treated by total cystectomy and radical excision of regional nodes

The clinical staging of any bladder tumour will depend on the evidence collected as the result of a clinical assessment (Fig. 38)

INVESTIGATION OF BLADDER TUMOURS

① Culture of urine — A sterile urine at the first examination eliminates the factor of sepsis



② IV Pyelogram

This may show — filling defects
renal function
stasis of ureter

③ Cystoscopy under anaesthetic

For Type — papillary or solid
Size — small average or large
Base — pedunculated or sessile
Surrounding mucosa.



④ Biopsy

Resectoscope | Cold Punch | Lowsley's or Riches forceps






⑤ Bimanual under anaesthetic

Complete relaxation and empty bladder



Palpable but mobile inside bladder



Palpable but infiltrating



Palpable but extravesical spread though still mobile in pelvis



Palpable but fixed to pelvis

FIG. 38 Clinical Assessment of Bladder Tumours. There are five main sections for a complete assessment. Omission of any one of these may mean inaccurate diagnosis. (From *Ann. Roy Col Surg Eng*)

Clinical Assessment

This method of grouping comparable cases together depends upon a clinical assessment of the spread of the tumour and upon a study of an adequate amount of tumour tissue removed for biopsy examination The clinical assessment depends on five main examinations.

1 *Culture of the Urine* A sterile cystitis may be the early symptom of mucosal carcinomatous.

2. *Intravenous Pyelogram* This may reveal abnormal kidney function, dilatation of the ureter or a filling defect in bladder or ureter

3 *Cystoscopy* The main features are size, surface (papillary solid or ulcerative), single or multiple lesions, pedunculated or sessile and the presence of abnormal mucosa.

4 *Biopsy Examination* Taken either by a resectoscope or by one of the punch instruments—Riches Lowsley s or the Thompson prostate punch

5 *Bimanual Examination under Full Surgical Anæsthesia* A few of the papillary tumours, especially the small ones, may be impalpable, but even the papillary tumours with early infiltration can usually be felt if sufficient care is taken during the examination. The bimanual findings may be classified as impalpable palpable but freely mobile within the bladder induration of the bladder wall but no evidence of tumour in perivesical fat, a nodular mass in the perivesical fat but still freely mobile, or a mass that is fixed to the pelvic wall Jewett (1946) was the first to emphasise the value of a routine bimanual examination under full surgical anæsthesia and he was also the first to draw attention to the importance of infiltration as the main factor in prognosis.

Histological Grading of Biopsy or Operative Material

The value of grading from biopsy material has been doubted by several authors. There are however several factors which may result in inaccuracy

Firstly the method A diathermy loop may result in charring of the material but an experienced resectionist will be able to pick the

site for taking the biopsy better with an instrument he knows rather than one with which he is not fully acquainted. Punch forceps may produce better specimens, but in the presence of bleeding it may be difficult to identify the best portion of the tumour for a biopsy with any of these instruments. Lowsley's forceps used in conjunction with a resectoscope sheath, is probably the best instrument for tumours of the posterior wall while Riches forceps is better for the trigone lateral or anterior walls

The second factor which affects the grading is the number of groups which are used Any classification having a large number of grades will have a lower correlation rate than a simpler classification with fewer grades

The third factor influencing grading is the personal variability of the pathologists so that if possible, grading of biopsy material and grading of tumour material should always be undertaken by the same pathologist

The Institute of Urology has suggested the following histological grades.

Papilloma. Where the fronds are delicate, the cell layer 3–4 cells thick the nuclei pale staining and regular the cell outlines well defined and of approximately the same size, and where the basement membrane is intact (Fig. 39)

Papillary Carcinoma Differentiated Where there is more disorder in cellular arrangement, where the cell layer is thicker and the regular palisade arrangement has been distorted, where the cells vary in size the nuclei stain irregularly and mitoses may be seen. Although it is not seen in every case, a breakthrough of the basement membrane of the papillary process is indicative of a papillary carcinoma rather than a papilloma (Fig. 40)

Papillary Carcinoma Anaplastic Where there is gross irregularity of the cell layer nuclei vary in shape, size and staining characteristics mitoses are common the basement membrane is broken through or cannot be clearly distinguished and the papillary processes themselves are misshapen and distorted (Fig. 41)

Solid Transitional Cell Carcinoma Differentiated Where the papillary differentiation has been lost but where there is a reasonably well-defined growing edge to the tumour where invasiveness is not

FIG. 39 Papilloma.

FIG. 40. Papillary carcinoma differentiated.

FIG 41 Papillary carcinoma anaplastic.

FIG 42. Solid carcinoma differentiated.

prominent, where the cells and nuclei arranged in a fairly orderly fashion are of approximately the same size shape and staining characteristics (Fig 42)

Solid Transitional Cell Carcinoma Anaplastic Where there is gross cellular irregularity prominent invasive characteristics, with no well-defined margin and where the nuclei vary in size, shape and in the intensity of staining (Fig. 43).

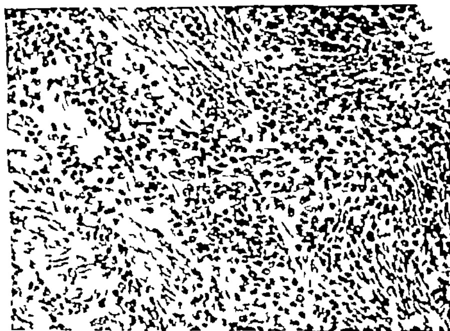


FIG. 43 Solid carcinoma anaplastic.

Squamous Cell Carcinoma There are cell nests keratinisation and prickle cells predominate. The general picture, however must be homogeneous throughout since a solid anaplastic tumour with metaplasia may mimic this histological picture. It is important to distinguish between these two types of tumour since the solid anaplastic disseminates rapidly while the squamous-cell carcinoma disseminates late and usually kills by local interference with kidney function.

Adenocarcinoma A relatively rare group—incidence reports vary between 0 4 per cent to 2 per cent of all cases. These may arise from the urachal remnant or as a result of glandular metaplasia. Adenocarcinoma is, however more frequently due to metastatic deposits from an extravesical primary tumour such as stomach, rectum, colon or prostate.

Clinical Stage

The clinical stage of a tumour depends on an assessment of all available evidence. If certain parts of the examination have been overlooked it may be that the clinical stage recorded will be under estimated

The Union Internationale contre le Cancre has suggested that the principles of clinical staging should be based on

T = evidence of direct spread of the *tumour*
N = evidence of invasion of regional *nodes*
M = evidence of distant *metastasis*

The bladder is not, however an organ whose regional nodes can be readily palpated and therefore the suggested staging is based purely on the evidence of direct spread, although when other information may be available it can be added under the appropriate section (Denoix, 1954)

Evidence of Direct Spread

Mucosal Stage (*T1*) The tumour is cystoscopically apparently confined to mucosa A mass, if palpable, is freely mobile inside the bladder The biopsy examination shows no evidence of infiltration and the intravenous pyelogram shows no dilatation of the ureter although slight stasis or delay is often associated with mucosal lesions (Fig 44)

Muscular Stage (*T2*) Cystoscopically there may be cicatricial bands on bimanual examination there is usually a diffuse, rubbery thickening involving a portion only of the bladder wall biopsy material may show evidence of muscular infiltration, and the pyelogram, should the tumour be situated near the ureteric orifice, will show moderate or gross dilatation of the ureter if the intramural portion is involved in growth (Fig. 45)

Perivesical Stage (*T*3). There is a discrepancy between the size of tumour seen cystoscopically and the size felt bimanually There is more tumour outside the bladder than inside. The external surface may be nodular and the mass is hard but completely mobile in all directions in the pelvis (Fig. 46)

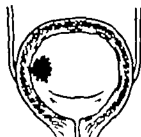


FIG. 44 Mucosal stage.

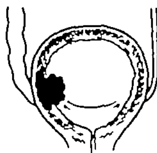


FIG 45 Muscular stage.

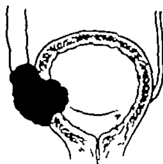


FIG 46. Perivesical stage.

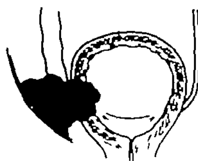


FIG 47 Pelvic fixation or involvement of adjoining organs.

Pelvic Fixation (*T*4) The involvement of scar or adjoining organs, or tethering of the growth to the anterior or lateral walls of pelvis usually means that the growth is unremovable, without hope of cure, although technically removable for palliative reasons only (Fig. 47) *

* The T N M staging can be amplified even at a later date, by the addition of information about nodes, Na impalpable, Nb palpable or N + or – histologically positive or negative, or by additional information about liver lung or bony metatases = M.

Other classifications that have been used are

Jewett (1946)

Stage A = mucosal
B_1 = superficial } muscular
B_2 = deep } muscular
C = perivesical.

Marshall (1956) (Fig. 48)

O = } mucosal
A = } mucosal
B_1 = } superficial } muscular
B_2 = } deep } muscular
C = perivesical
D_1 D_2 = any stage with nodal involvement local or distant

Dukes Masina (1949)

Ia = mucosal
Ib = muscular
2 = perivesical
3 = perivesical with glands
4 = pelvic fixation or any stage with metastases or more than regional node involvement.

Riches (1956)

A = mucosal
B = muscular and perivesical
C = perivesical with nodes or pelvic fixation.

Poole-Wilson (1954)

Superficial = mucosal and muscular
Advanced = perivesical

The need of a uniform classification is paramount to enable comparison between series of cases. The T N M. International would appear to fulfil this need.

Bladder Tumours as an Industrial Hazard

As there has been a considerable increase in the incidence of bladder tumours in the younger age groups the question of industrial or environmental factors must be considered in all cases of tumour It has now been realised that the "aniline dye-stuff workers" are not unique in the liability to contract bladder tumours, and that the

risk is not due to the aniline as such but to the use of intermediate chemicals in the dye processing It is these compounds mostly aromatic, amino and basic in form (Goldblatt 1947), that are responsible for the production of bladder tumours, since other industries are also *finding bladder tumours in the workers exposed* to these chemicals The full occupational history of any patient

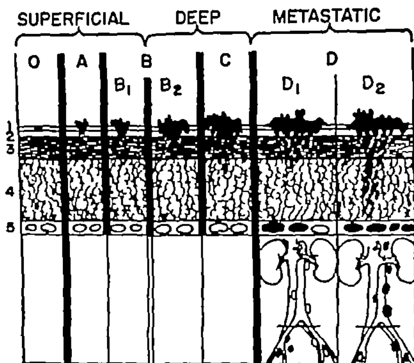


FIG 48 Marshall's clinicopathological classification. This staging can only be fully applied to cases treated by radical surgery when both nodes and bladder are available for pathological study (Copied from *Cancer*)

with bladder tumours should be taken as a routine procedure, for although a sudden strong exposure to a chemical may produce symptoms of cystitis with hæmaturia very rapidly there is usually a long latent period between the first exposure and the development of a tumour In the case of β-naphthylamine it is usually many years.

Although the production of β-naphthylamine has been stopped in Britain it is still being produced abroad while benzidine and

xenylamine are both readily obtainable and are being used in a considerable variety of industrial products.

Melick (1954) in a recent paper has reported an incidence of 11 per cent of bladder tumours in workmen exposed to xenylamine, a chemical which was forecast as a possible carcinogen by Case (1954), and Walpole, Williams and Roberts (1952). Benzidine, also a constituent of dye processes, is a well-recognised carcinogenic risk, so much so that bottles of this chemical are prominently labelled as carcinogenic by the manufacturers

TREATMENT OF BLADDER TUMOURS

By far the greater number of bladder tumours can be treated by perurethral means either by endoscopic resection using the loop or the punch, or by coagulation. The point at which various surgeons will select other methods will depend on multiplicity of tumours and infiltration The presence of infiltration into the muscle layers is usually taken as a contra indication to further endoscopic surgery A bladder mucosa which is grossly abnormal, the site of multiple tumours both in space, i e. occurring simultaneously or in time, i.e. occurring at different sites over a period of time, may be considered as unsuitable for further endoscopic therapy

Milner (1953) and Chapman (1954) have both produced series of cases showing what can be achieved by endoscopic methods.

Multiple mucosal tumours with areas of abnormal mucosa, often incorrectly termed papillomatosis, are usually considered to be beyond adequate control by diathermy These cases may be treated by either total cystectomy of by some form of irradiation. Total bladder irradiation by external therapy has been advocated, but satisfactory statistics are not yet available. It is, however well recognised that external irradiation can effect a complete disappearance of these tumours in an appreciable percentage of cases.

Intracavitary Irradiation

The insertion into the bladder of radioactive material has been tried now for some years. These sources may consist of solid radium

or cobalt placed in the centre of an air filled balloon, or solutions of radioactive sodium, bromine, gold or yttrium (Freedman 1949 Wallace, Walton Sinclair 1949 Ellis, 1955) The use of a solid material such as radium or cobalt is undoubtedly safer for the staff handling the material, but unless the central source is, in fact, central more radiation may be given to the normal parts of the bladder than is received by the tumour base. In addition the rate at which the radiation falls off i.e. the depth dose curve, is slow so that not merely the mucosa but the muscle and perivesical tissues, may all receive a high dose.

The effectiveness of radiation depends on being able to deliver a sufficient number of Röntgen units to the tumour while conserving the normal tissue as far as possible The method of intracavitary irradiation using solid sources, because of the necessity for the bead to be central and because of the gradual falling off in the depth dose curve, does not conform to a good technique for mucosal tumours

Solutions inserted into a balloon in the bladder obviate the necessity for the source to be geometrically central, since the dose delivered can be measured from the surface of the balloon. The risk of rupture of the balloon, although in practice minimal, is a real one and if the solution has a long half life (cobalt) contamination of the bedroom, clothing, etc., may have serious consequences Solutions of bromine or sodium have a short half life, and also a much more rapid falling off in the depth dose curves, so that using either of these two solutions it is possible to deliver a higher dose to the mucosa than to the muscle or perivesical tissues

All methods of intracavitary irradiation that employ a balloon are open to the criticism that the surface of the tumour will receive the same dose as the normal mucosa over the rest of the bladder while the base of necessity pushed away from the surface of the balloon by the mere bulk of the tumour will receive a dose that corresponds to that of the muscle in the healthy part of the bladder (Fig. 49). Unless the radiosensitivity of the tumour is much greater than the radiosensitivity of the muscle, a dose of irradiation that will destroy the base must inevitably produce changes in the muscle.

Instilling a radioactive colloidal solution into the bladder without a balloon has considerable theoretical advantages since a fronded lesion will project into the solution and the fronds will, therefore, be irradiated on both sides If a colloidal solution is used the risk of absorption is minimal, and if the radioactive material (gold, yttrium) is mainly a beta emitter only a very superficial treatment will be given. The conservatism of the muscle of the bladder wall, and the

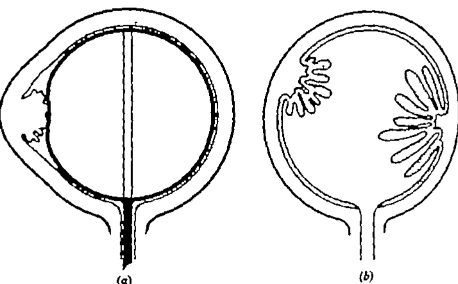


FIG. 49 Intracavitary irradiation with isotope solutions.
(a) *Balloon* base of a bulky tumour is displaced out of zone of effective irradiation.
(b) *Colloidal solution.* Solution permeates between fronds but leaves small volume at base of a sessile tumour unirradiated.

prevention of changes in the arterioles of the submucosal layers are both important if post-therapy morbidity is to be avoided

Interstitial Irradiation

The treatment of single tumours of the bladder which have begun to infiltrate but have not yet spread through the bladder wall (T2) can be treated either by partial cystectomy or by interstitial irradiation

Interstitial irradiation can be divided broadly into two main

groups the removable implant such as radium tantalum (Fig 50) or cobalt wire and the irremovable implant such as radon gold grains or chronic phosphate solution

Radium is readily available and can be used even in the smallest centres, but whether the results obtained warrant universal use is debatable (Higham, 1955 Darget 1951)



FIG. 50 X-ray of tantalum wire inserted into base of tumour

Tantalum is a flexible wire coated with platinum to filter off the β-radiation It may be regarded as "flexible radium" since it can be introduced by means of a twin boomerang needle into the base of a tumour and subsequently withdrawn down the urethra (Fig. 51) With a long half-life (four months) it can be always available even at short notice (Wallace, Stapleton, and Turner 1952)

Cobalt wire sheathed in nylon tubes is again flexible and can be darned through the base of a tumour being subsequently removed

by traction. The bulkiness of a nylon sheath, which is required for the elimination of β-radiation, renders the cobalt sutures more cumbersome than the tantalum wire where the filtration is effected by platinum (Vermooten, 1955)

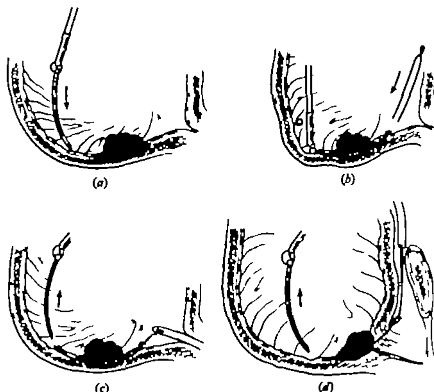


FIG 51 Insertion of tantalum wire.

(a) Needle inserted into bladder wall clear of the edge of tumour
(b) Needle in position in bladder wall—hairpin of tantalum being inserted.
(c) Needle withdrawn—tantalum lying in bladder wall and loop tied to urethral catheter
(d) Wire inserted for tumour on anterior wall or bladder neck, via retropubic space—withdrawn with retropubic drain.

One of the criticisms levelled against interstitial implants is that frequently the tumour is completely removed by diathermy loop excision prior to implantation and, therefore the result may be due to the excision and not to the implants Several cases have been

treated by tantalum wire alone without excision of the tumour and complete tumour regression has occurred

The irremovable implants—radon seeds or gold grains—have one common disadvantage in that when a technically bad implant is made and the radioactive sources are placed too far apart an area of bladder wall will be under irradiated and a local recurrence will be inevitable if active tumour tissue was present at this point.

This lack of control of the amount of irradiation is not present in the removable implants, which can be left *in situ* for a longer time if necessary Both radon seeds and gold grains generally remain *in situ* once they have been inserted, unlike colloidal gold or chromic phosphate which when injected into a tumour may remain there or may diffuse into the surrounding tissues The infiltration technique cannot be checked for radiation distribution by post operative X-rays as the solutions used are not radio-opaque. Extremely good results may be obtained in the hands of persons experienced in the technique of implantation provided the selection of cases is strict, and tumours which have spread through the bladder wall are not treated by these methods (Millen 1950).

External Therapy

The role of external therapy is still not clearly defined. Super voltage plants of two million volts or more can undoubtedly deliver a very large dose to a volume deep in the pelvis and would, therefore, be suitable for perivesical tumours that were unsuitable for other treatment. This method of treatment causes minimal skin reaction or untoward side effects provided the dose is given over a sufficiently long period Unfortunately it is these perivesical tumours that are most likely to have spread to lymphatic glands and, although super voltage therapy may control the primary tumour the outcome of the disease may be decided by the metastases

Supervoltage therapy can be used for irradiating the pelvic walls in cases where the primary tumour has been removed by local surgery It may well be that this combination of surgery followed by supervoltage therapy will prove to be the most efficacious combination.

Partial Cystectomy

Partial cystectomy or as it is also sometimes called, segmental resection is viewed with disfavour in certain clinics, largely due to the disappointing results that have been reported over recent years. Where, however, a correct selection has been made, and where care has been used to operate only on cases that conform to the criteria detailed below the results are comparable, if not better than the results of cases treated by more radical methods (Manna, 1953).

The ideal case for partial cystectomy must be a single lesion showing no evidence of abnormal mucosa, patches of hyperplasia or a second seeding lesion The margins of the growth should be well defined, without any suggestion of submucosal spread. The position of the lesion should be such that a clear margin of at least an inch can be obtained between the line of section and the histological edge of the tumour

The main contra-indications to partial cystectomy are multiple tumours, or evidence of mucosal instability throughout the bladder, or a tumour with an edge so ill defined that it is impossible to say where tumour ends and normal bladder wall begins.

The multifocal tumours are evidence of a mucosal disease and any method that fails to treat the entire disease field is doomed to failure. A tumour with an indefinite margin is frequently of a relatively anaplastic type, tending to spread by veins or lymphatics under the mucosa for a considerable distance. Any form of conservative surgery in these cases may be inadequate, since the line of section may transgress the tumour substance. In general it may be added that tumours on or near the base of the bladder are unsuitable for partial cystectomy since an adequate excision in this region which may necessitate re-implantation of one or both ureters or reconstruction of the internal meatus, is rarely achieved.

Operative Detail

Partial cystectomy is an operation that must be planned well in advance. At the cystoscopy under anæsthesia the probable lines of excision should be planned, especially in relation to the ureteric orifices and the internal meatus Unless an adequate margin can be anticipated all hope of conservative surgery should be abandoned.

At the time of the cystoscopy too especial care should be directed to the mucosa at the base of the tumour and also in the remainder of the bladder since it is only if the lesion is strictly localised that conservative surgery can be justified

Partial cystectomy may be commenced with a bladder distended or empty The distended bladder may make dissection easier but carries a greater risk of spillage of tumour cells. A preliminary laparotomy should be undertaken in every case with inspection or palpation of the liver para-aortic nodes, peritoneal surface of the bladder and pelvic nodes It is only after confirmation of the operability that the bladder should be opened. It should never be necessary to open the bladder in order to assess operability or even to establish the diagnosis

Total Cystectomy

Total cystectomy that is removal of bladder prostate, seminal vesicles and all the paravesical tissues, but not including a block dissection of the iliac nodes has certain well-defined indications which are accepted in the majority of clinics It must be remembered, however that this operation carries not merely a high operative risk but also a high morbidity rate in the post operative period A mortality rate of 10–20 per cent must be expected if this operation is to be offered to all those that might benefit a lower mortality rate may be an indication of too stringent selection, while a higher mortality rate is indicative of attempts to achieve the impossible.

The operation of total cystectomy is inevitably severe and should only be offered to the elderly when there is no other method of relieving symptoms. In the younger age groups the almost certain loss of potency may be an argument against too facile recommendation of the operation

Indications

The indications for total cystectomy vary among different clinics Some authors believe that only by performing radical extirpation of the disease at the earliest opportunity will the results be improved.

Others prefer to employ conservative methods first and cystectomy *only when other methods have failed* *It is, however obvious that* only when the limitations of the various conservative methods are appreciated and only when the natural histories of the more malignant types of the disease are understood will total cystectomy be placed on a proper footing

In brief however the following are taken for the main indications for cystectomy (Riches, 1956)

(1) Large, bulky non infiltrating tumours beyond the scope of cystoscopic diathermy too bulky for intracavitary irradiation, too extensive for interstitial irradiation and where, owing to the widespread nature of the disease, open diathermy runs the risk of wound implantation.

(2) Infiltrating tumours of the bladder base where the stage is more than muscular or where the prostate or posterior urethra are involved especially if there is evidence of multifocal origin such as areas of hypertrophic mucosa or cystitis cystica or glandularis. Infiltrating tumours of the vault or even muscular tumours occurring with prostatic obstruction are also best treated by radical excision. Involvement of the bladder by growths of adjacent uterus, colon or rectum, cannot be treated in any other way than by total cystectomy

Total cystectomy may be a life-saving measure in cases of really severe hæmaturia where, in spite of all other methods, the bleeding is uncontrolled. It is infinitely better than opening the bladder blindly in the hope of applying diathermy to a lesion which is usually infiltrating. Radio-necrosis or the bleeding that sometimes occurs after external X ray therapy where there are changes in the arterioles or atrophy of the mucosa, may necessitate cystectomy even when the *bladder is* tumour free. Cystectomy is also indicated when a tumour has been treated by local interstitial irradiation and subsequently a second tumour develops in another portion of the bladder sometimes of a completely different histological type.

Finally when a palliative transplantation of the ureters, even if supplemented by external high-voltage therapy has failed to relieve symptoms, a purely palliative removal of the bladder may be justified

Total Cystectomy, Operative Technique

The modern technique of total cystectomy is based on the description by Millin and Masina (1949) The pre-operative care of the patient includes full biochemical and radiological studies. The toilet of the colon has been simplified by the use of chemotherapeutic and antibiotic drugs, one of the most popular now being a combination of sulphaguanidine and streptomycin given orally three times a day for three days before operation. A high colonic wash-out may be given daily for several days before operation but never on the day of operation lest the fluid be incompletely evacuated pre-operatively

The bladder is emptied at the beginning of the operation and a formal laparotomy carried out with careful palpation of the iliac and para aortic nodes, the liver and both kidneys If the operation is to be completed in one stage the ureters are defined, sectioned as low as possible and rubber catheters inserted so that urine will drain away from the operative area. There is no harm likely to follow if at this stage the internal iliac arteries are tied on each side as in an abdomino-perineal excision of rectum. This step minimises the bleeding from superior and inferior vesical pedicles The peritoneum is then incised along the pelvic brim to the site of the ureters and joined as low in the recto-vesical pouch as possible. At this point it is as well to remember that the object of the operation is to remove not merely the bladder but all the perivesical tissue, and that to achieve this the block of tissue removed should be thick enough to prevent identification of the bladder wall. A simple method of dissecting down to the vesicles consists of following the obliterated hypogastric artery to where it crosses the vas, then to dissect between the vas and the peritoneum to the crossing with the ureter then to trace the ureter to the seminal vesicles. Between the seminal vesicles there is a layer of fascia which is incised to open into the space of Proust (Fig. 52). This space leads forward to the apex of the prostate The vesical pedicles are clamped and cut and finally the bladder is tethered only by the two puboprostatic ligaments on either side of the urethra. When these are cut the apex of the prostate can be drawn upwards with resultant elongation of the urethra. With the index finger behind the apex of the prostate and

the thumb in front pressure is applied to the apex and the urethra cut. This manœuvre is more certain to prevent accidental spillage from the urethra than any clamp yet devised

It is rarely possible, if an adequate excision has been achieved, to

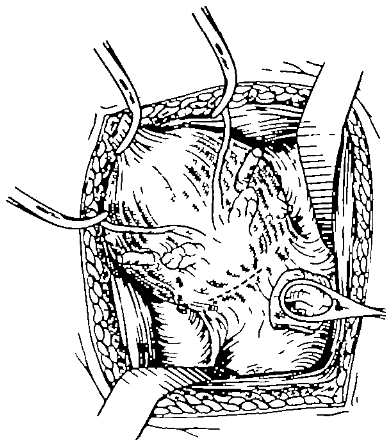


FIG 52. Exposure of bladder base at total cystectomy showing vasa, ureters and vesicles. Incision between vesicles opens into space of Proust.

reperitonealise the pelvic floor In many clinics it is believed that a wide open pelvis is less likely to strangulate a loop of intestine than a tense diaphragm, perforated possibly with multiple small apertures through which a loop of bowel may prolapse.

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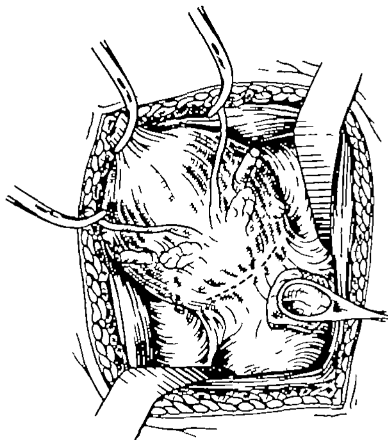


FIG. 52. Exposure of bladder base at total cystectomy showing vasa, ureters and vesicles. Incision between vesicles opens into space of Proust

reperitonealise the pelvic floor In many clinics it is believed that a wide open pelvis is less likely to strangulate a loop of intestine than a tense diaphragm perforated possibly with multiple small apertures through which a loop of bowel may prolapse.

The ureteric transplantation is customarily left to the last since the delicate stitching and the exact accurate approximation without tension of the colon to the ureter can easily be disarranged if undertaken too early in the operative plan

Radical cystectomy—that is, the removal of bladder prostate and vesicles and also all the lymph nodes of the pelvic walls up to the bifurcation of the iliac arteries is more in keeping with cancer surgery elsewhere, but it is an operation that is practised in relatively few clinics (Marshall 1956) Whether the removal of all the lymph nodes compensates for an inevitably higher operative mortality must await assessment in years to come.

Possible Ætiological Factors of Bladder Tumours

The ætiological factors and natural history of bladder tumours have been investigated by many centres. The older theories have been based on the "seedling" mechanism, the idea that exfoliated cells from a tumour could implant on intact mucosa. MacDonald (1956) has shown that this can in fact, occur in an empty defunctioned pouch of bladder and several authors have supported this possibility but in the majority they have qualified the seedling theory by postulating the presence of abraded or traumatised mucosa on to which the exfoliated cells adhere (Boreham, 1956 Ashworth, 1956) There is no doubt that implantation from a papillary tumour can occur readily in the presence of a traumatised mucosa implantation into a wound can equally readily occur but in both cases the exercise of meticulous care and gentle handling of the tumour using every aid to prevent scattering cells, can result in wound implantation being reduced to minimal proportions

The alternative theory to the seedlings mechanism is based on a series of clinical observations.

Papillary bladder tumours may be multiple in space, i e. multiple tumours present at one moment of time over the whole bladder

Papillary tumours may be multiple in time, i e. multiple tumours involving the whole bladder but appearing over a period of years.

Papillary tumours may co-exist with areas of widespread epithelial hyperplasia or mucosal changes.

Papillary tumours of the bladder may co-exist with similar lesion of the kidney the kidney lesion may precede the bladder lesion or it may develop after the bladder lesion

Papillary tumours may be of different histological types, existing together in the bladder at one moment in time.

Papillary tumours have been recorded as apparently undergoing spontaneous remission after transplantation of ureters.

Industrial bladder tumours due to exposure to either β-naphthylamine, benzidine or xenylamine are indistinguishable from those tumours which appear to arise spontaneously

The urogenous (or water borne factor) theory is based on the *supposition that there might be an irritant—possibly of a chemical* nature—in the urine which bathes the entire mucosa and initiates a field change over the whole of the urinary tract. If this were true it would explain the presence of mucosal hyperplasia occurring in many places in the bladder before the appearance of a tumour These changes, sometimes taking the form of a mossy hyperæmic mucosa, cannot be explained by the seedling theory By analogy with the known industrial tumours it might be supposed that this factor would have some resemblance to the metabolites of β-naphthylamine or to similar carcinogenic compounds, all of which are basic, amino and aromatic in structure.

Experimentally the evidence for the urogenous theory is considerable, based largely however on work with β-naphthylamine. The original observation by Hueper Wiley Wolfe (1938) that after transplantation of the ureters, feeding dogs with β-naphthylamine will no longer cause production of bladder tumours, was of fundamental importance. Scott (1953), repeating these experiments, confirmed the findings but, in addition, in one animal which developed a stenosis at the uretero-colic anastomosis with hydro-ureter and hydronephrosis, a papillary tumour developed on the ureteric mucosa at the site of maximum stasis

MacDonald (1954), by dividing the bladder into two halves each with the same blood, nerve and lymphatic supply but only one half in contact with urine, was able to demonstrate that only the bladder mucosa in contact with the urine was liable to develop tumours. In one of his dogs a fistula developed between the two pouches and in

this animal tumours also appeared in both portions of the bladder

Bonser (Bonser *et al* 1954) by developing a technique for implanting pellets into the bladders of mice was able to show that β-naphthylamine only rarely produced tumours, but that its unconjugated metabolite, 2-amino-1 naphthol was highly carcinogenic. This experimental evidence all points to the presence in the urine of a chemical, more simple in form than β-naphthylamine, acting directly on the bladder mucosa.

The similarity between the industrial and spontaneously occurring tumours led to a search for some similar agent in the urine of the spontaneous tumour patients. The experimental evidence of Boyland Harris and Horning (1954) indicates that the metabolites of tryptophan could apparently produce tumours of the urinary tract, especially if these were excreted in conjunction with other similar substances of a more general carcinogenic nature. The metabolic products of tryptophan kynurenin hydroxykynurenin anthranilic and hydroxyanthranilic acids are all amino aromatic and basic in form and resemble the 2-amino-1 naphthol chemical structure very closely These chemicals have all been found in considerably increased amounts in the urine of patients with bladder tumours, especially multiple tumours by Boyland (1956) and Price (1956 personal communication) of Wisconsin. The normal urine contains, if any only a trace of the substances.

These chemicals have also been shown to be carcinogenic by direct implantation into the bladders of mice, using a simplified form of the Bonser technique (Boyland and Watson 1956) These chemicals would normally be excreted in a detoxicated form in conjugation with a glucuronide, but it has been shown that urine from bladder tumour cases contain large amounts of the enzyme glucuronidase which, in the presence of stasis or concentration splits the conjugated compound to release the free acid

Although the evidence is recent it is accumulating. In at least some types of bladder tumour there may be a factor—probably a free aminophenol compound—which is responsible for the initiation, if not the maintenance, of multiple tumours. This may well be the factor responsible for "recurrences" over subsequent years if it is not suppressed or diluted.

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CHAPTER 10

DIVERSION OF THE KIDNEY URINE

Including Artificial Bladders

It is frequently necessary to divert the urinary stream from its usual channels before performing various operations. The choice of the methods used depends upon the site of the pathology and upon whether the diversion is to be temporary or permanent.

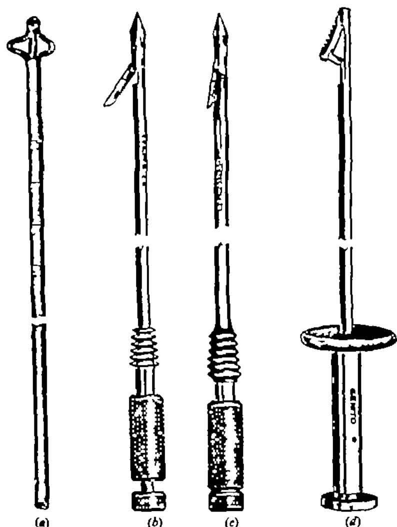
The results of extensive plastic operations upon the penis and urethra for hypo- or epispadias, etc., are greatly improved if the urine is diverted from the suture lines. For this purpose, perineal urethrostomy or suprapubic cystotomy are both suitable.

Perineal Urethrostomy

A perineal opening provides the most dependent bladder drainage possible (Sandrey 1948) and also the ideal route for endoscopic resection of the prostate when there is any doubt at all about the narrowness of the penile urethra and external meatus. However if drainage has to be maintained for more than a few days, its disadvantages outweigh its usefulness. The patient cannot walk about in any degree of comfort and in these days of early ambulation this is an important factor One argument in favour of the perineal drainage is that the suprapubic area is left clear for further surgery It can also be performed upon an empty bladder whereas all the forms of stab cystotomy require a palpably distended bladder if they are to be safe.

Riches Suprapubic Catheterisation

This procedure, devised by Riches (1943) for use in a spinal injury centre, is ideal for all cases requiring temporary bladder drainage, and especially for the relief of prostatic urinary obstruction in frail old men suffering from cardiovascular diseases It can be performed on the distended bladder under local anæsthetic, and allows of



(a) (b) (c) (d)

FIG. 53 Riches Suprapubic Catheterisation Apparatus.
(a) Special catheter
(b) Trocar showing blade open.
(c) Catheter gripped and stretched over the trocar
(d) Catheter advancer

immediate ambulation Owing to the narrowness of the tube it is not suitable for long periods of drainage in out patients In a majority of cases it causes no retropubic inflammatory reaction so that subsequent surgery such as retropubic prostatectomy is not impeded (Scorer 1953)

Technique

Suprapubic catheterisation differs from the set suprapubic cystotomy or stab cystotomy *in that the catheter forms its own* cannula (Fig. 53) A long trocar fits inside a special soft rubber catheter the tip of which is gripped by an ingenious knife-edged device, thus allowing the catheter to be stretched and reduced in diameter When the distended bladder has been defined above the pubis a half inch skin incision, with a similar division of the under lying fibrous sheath, suffices to introduce the trocar and catheter into the bladder Release of the special catch enables the catheter to expand, creating a water tight junction through the bladder wall and allowing the trocar to be withdrawn A special advancer is used to push the catheter well down inside the bladder so that as the latter empties and contracts away from the abdominal wall the catheter will still remain *in situ*

DIVERSION OF KIDNEY URINE

One of the greatest unsolved urological problems today is that of diverting the urine before it reaches the bladder Nephrostomy and cutaneous ureterostomy drainage, though uncomfortable for the patient, are relatively simple to perform and are certainly safe. However the ideal would be some method of draining the urine into the bowel so that the anal sphincter could be used to maintain continence. Unfortunately ureterocolic anastomosis carries the real risks of obstructive back pressure and ascending renal infection combined with electrolyte imbalance, and it must be admitted that, in spite of extensive trial and a multiplicity of operative techniques, this ideal is not yet in sight, so that urologists are now turning their attention to the possibility of forming artificial bladders using isolated intestinal loops. However until more experience is gained in this field, uretero-intestinal anastomosis or cutaneous uretero-stomy will continue to be used under certain conditions.

Cutaneous Ureterostomy

This is a much simpler and safer surgical operation than uretero-colic anastomosis but it has the great disadvantage of a fistulous opening on the abdominal wall while an efficient but simple collect

ing apparatus has yet to be designed There is also a tendency for the ureter to slough away between the muscles and the skin surface or at least for the stump to retract considerably Even so there is practically no operative morbidity or mortality while electrolyte problems do not occur Since urologists are tending to accept the necessity of a skin fistula in their search for an artificial bladder it may well be that cutaneous ureterostomy will return to favour if the problem of stricture formation can be overcome

In the past it has always been stated that once a cutaneous ureterostomy—always a cutaneous ureterostomy" but this is certainly not true, and there are numerous reports in the literature of re-implantation into the bowel (Beisler 1948) while Rack (1953) and his colleagues used a cutaneous ureterostomy as a temporary measure. They had used a Foley catheter to drain an isolated ileal loop bladder but after eighteen days it caused uncontrollable hæmorrhage so that the ureters had to be placed on the skin temporarily until a new ileal bladder could be made. They were able to overcome the shortness of the ureters in the final operation by utilising Y loops of ileum.

There are two schools of thought about collecting the urine from a skin ureterostomy Some surgeons prefer an indwelling catheter up to the renal pelvis and unless special precautions are taken over the stoma, this is the safest procedure. Others rely on some form of cup collecting apparatus fitting tightly on to the skin and use no ureteric catheter

On principle, one wishes to avoid a ureteric catheter if possible, and the recent introduction of efficient adhesive bags of the Rutzen type may alter the urological approach to this problem. For example, recent attempts have been made to fashion projecting nipples or stumps which will fit into various types of collecting devices If the ureter is brought to the tip of these skin stumps retraction can be controlled and the fitting of an apparatus is simplified

Abeshouse (1948) devised techniques for making such a stump and the details are shown in Fig. 54 but there are others in the literature about the same time (Schinagel and Sewell 1948 Goldstein and Berman 1944)

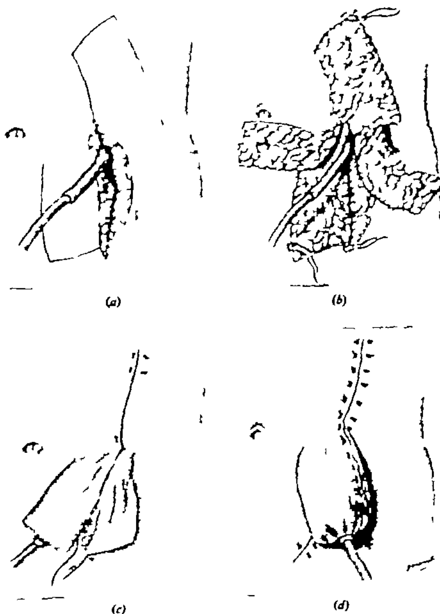


FIG. 54. Steps in the formation of a "pedicle" or "spout" cutaneous ureterostomy

More recently Fish and Stevenson (1949) devised a pedicle graft cutaneous ureterostomy which shows less tendency to contracture than most, although a two-stage operation is necessary The pedicles are made from a full-thickness flap measuring approximately 3 by 5 inches, and lie just above the normal belt line at the outer edges of the rectus muscles. At a second operation the ureters are isolated through lumbar incisions divided close to the bladder and drawn through the abdominal muscles to project at the tip of the pedicle. This latter manœuvre is achieved by inserting a scalpel down the finger like pedicle from its tip, and pushing it through the abdominal muscles as a stab wound The free end of the ureter is now tied to the neck of the scalpel which is drawn back along its original track.

The mucosa of the ureter is sewn to the skin of the tip of the pedicle and is the only fixation used No indwelling catheter is required, but a collecting cup is easy to attach to the finger like pedicle.

Vose and Dixey (1953) have developed a method of permanent or temporary ureterostomy by means of simple intubation The ureter is exposed in its middle third but is not disturbed other than by a small incision through which a tube is passed up to the pelvis The track becomes lined with granulation tissue which tolerates the catheter well while it is claimed that the changing of tubes is a simple procedure. This sounds attractive, but no long term follow-up results are yet available

Indications for Uretero-Intestinal Anastomosis

Congenital anomalies such as ectopia vesicæ do well after uretero-intestinal transplantation and many successful long term results have been reported. Severe trauma to the bladder or urethra causing permanent fistulæ or strictures can be given a comfortable existence, but in cancer cases, which form the great majority of those requiring urinary diversion, the results are disappointing.

The problem to be overcome is the formation of an artificial anastomosis between the ureter and the gut which will be wide and supple enough to allow urinary drainage without undue back pressure,

but which at the same time will have sufficient sphincter action to prevent regurgitation of infected material up the ureter

Broadly speaking, if the ureter is inserted into the bowel as a projecting stump (the simplest and safest operative procedure) the stump may later slough causing a stricture, while if it remains wide open regurgitation will occur To avoid regurgitation the ureter can be buried under the muscularis for a centimetre or more before it opens into the bowel, thus creating a valve action (Stiles, 1911 Coffee, 1931 Grey Turner 1938) but stricture formation at the ostium is still common.

In an effort to avoid stricture formation mucosa-to-mucosa junctions have been devised (Cordonnier 1950 Nesbit, 1948) and have been combined with a submucosal bed (Leadbetter 1951) in an attempt to produce a valve action as well The Leadbetter operation is the ideal in theory but it must be admitted that it is difficult, and therefore sometimes unsafe to perform unless the ureter is dilated If the ureter is grossly thickened as well as dilated (as in cases of systolic bladder following tuberculosis, etc.) a cutaneous uretero-stomy may be a much safer procedure, since regurgitation from the gut is certain under such circumstances.

Uretero-colic Anastomosis

Well over fifty methods of joining the ureter to the colon have been described in the literature, all designed to overcome the three great dangers associated with this operation, namely leakage of urine or fæces through the suture lines, delayed stenosis of the ostium and regurgitation of colonic contents into the renal pelvis.

The multiplicity of operations alone shows that the ideal method has not been devised, and only four or five types of operation are in present-day usage. Until the introduction of the mucosa to-mucosa techniques in 1948 the Stiles (1911) and Coffey (1911 1931) operations held the field. In both cases the ureter is introduced into the bowel lumen for a centimetre or more and held by a fixation stitch brought out through the bowel wall In Stiles operation (Fig. 55) the junction is buried by bringing the whole thickness of the bowel wall together round it with interrupted sutures. In the Coffey

operation (Fig. 56) the ureter lies in a submucosal bed under the sero-muscular layers before opening into the lumen This tends to produce a valvular opening which it is hoped will reduce regurgitation but

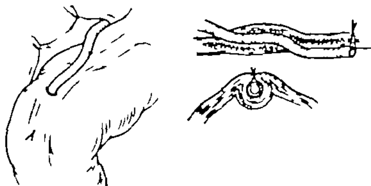


FIG. 55 *Stiles operation.* The ureter is buried in the whole thickness of the bowel wall.

both of these operations are prone to stenosis of the projecting ureteric stump, probably due to its poor blood supply

In 1948 Nesbitt described his direct mucosa-to-mucosa operation (Fig. 57) The ureter is split for 1 5 cm. and the corners cut off to

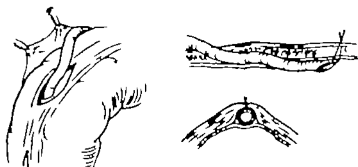


FIG 56. *Coffey operation,* where the ureter lies in a submucous bed under the sero-muscular layers before entering the gut.

form an elliptical opening which is then joined to a similar opening in the gut. The continuous suture takes in all layers of the ureter and sigmoid in such a way that the mucosal surfaces are everted and in contact.

In Cordonnier s operation (1950) (Fig 58) the gut is brought over and fixed to the opening in the peritoneum exposing the ureter so

that only a short length of the latter need be mobilised. Avoiding a tænia if possible, a sub-mucous trough is now prepared in the sigmoid in the depths of which a direct mucosa-to-mucosa anas-

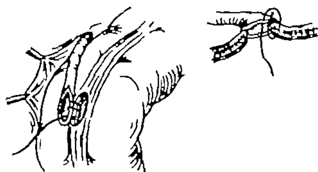


FIG. 57 *Nesbitt operation.* Approximation of mucosa to mucosa by sutures taking in the full thickness of the sigmoid wall.

tomosis is made using interrupted sutures. A second row of sutures fixes the seromuscular layer of the gut to the adventitia of the ureter in such a way that the stump projects into the lumen of the sigmoid, but has a mucosa to-mucosa junction.



FIG 58 *Cordonnier operation* using direct mucosa-to-mucosa anastomosis by sutures through the bowel mucosa in the depths of a seromuscular pit.

Both of these techniques reduce the tendency to stenosis of the ostium but still allow of regurgitation and in an attempt to over come this latter problem Leadbetter (1951) introduced his modification using a longitudinal mucosa-to-mucosa junction which is buried in a submuscular tunnel, thereby creating a valvular mechanism (Fig 59)

The opinion among British urologists is that the open mucosa to-mucosa operations are too often followed by ascending infection and that theoretically the Leadbetter operation is the best and should be performed when possible. However it takes much longer to

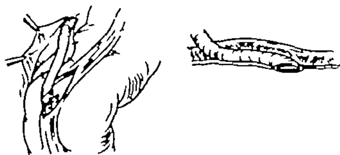


FIG 59 *Leadbetter technique* combining a mucosa-to-mucosa junction with a submucular tunnel.

carry out than a Stiles or Coffey procedure, and would appear most suited to cases where the ureter is slightly dilated

Vesicorectostomy

Moore (1954) has reported a method of urinary diversion which he asserts can be used for cases of urethral stricture and carcinoma, urethral incontinence, and for severe Hunners ulcer or the systolic bladder of healed tuberculosis The principle consists of making a fistula between the rectum and the trigonal area of the bladder in the triangle bounded by each vas deferens and the rectovesical pouch

In the first stage of the operation, the bladder and rectum are stitched together around the proposed site of the fistula, this manœuvre being aided by an assistant s thimble protected finger in the rectum The urethra is closed just distal to the verumontanum. The bladder is drained suprapubically for a fortnight, after which a piece of tissue is excised right through to the rectum. Using long curved forceps, a tube is drawn through the anus into the bladder and fixed with a Harris stitch, after which the bladder is closed.

Only two cases are reported (a complete epispadias and a urethral stricture with multiple perineal abscesses and fistulæ) but they have been followed up for five years Moore claims that no upper urinary

tract dilatation or electrolyte imbalance has occurred although was only based on clinical examination in one case. He attrib the lack of absorption to the fact that the urine is diverted into rectum below the rectosigmoid junction where he believes there competent sphincter which prevents the urine reaching the sigr colon This operation must be regarded as experimental work, the urge for such ingenuity illustrates the general feeling of satisfaction with all of the present methods of diverting urine f the normal channels

Late Results of Uretero-colic Anastomosis

The late results of uretero-intestinal anastomosis in 1 637 pati operated upon by British urologists have been reviewed by Jac and Stirling (1952) who showed that the overall operative morta was 21 per cent. The risk was much greater in cancer patients whom 40 per cent of 476 cases died from the anastomosis alo before a cystectomy could be performed Transplantation trauma or congenital anomalies produced a mortality of only 10 cent and 11 per cent respectively

The Coffey operation appeared to be the safest procedure with immediate mortality of just under 20 per cent, but they conclu that the nature of the lesion rather than the mode of techni was thus the major factor influencing immediate results.

Complications

The three major problems following ureteric implantation leakage, ascending urinary infection and delayed stenosis of ostium.

Leakage at the site of anastomosis is probably the chief danger the operation, since by causing an excessive local inflammato reaction the risk of stenosis and ascending infection are grea increased. In the Jacobs and Stirling review ileus, peritonitis, fistu and burst abdomen all of which could be attributable to some degr of leakage, accounted for over 55 per cent of the total complicatio

Ascending Urinary Infection. *This is almost inevitable to so* degree unless a perfectly functioning valvular opening has been mad

The regurgitation of intestinal gas or opaque medium up into the renal pelvis can be demonstrated radiologically in some patients particularly in the direct implants where in one series it occurred in nearly 50 per cent of the cases (Jacobs and Stirling 1952)

Contracture of the Stoma. This complication is more common following the technique where a stump of ureter projects into the bowel lumen than in the mucosa-to-mucosa methods. The Leadbetter operation would appear to offer the best compromise between regurgitation and contraction

Biochemical Changes Following Uretero-intestinal Anastomosis

The long-term results of uretero-intestinal anastomosis will vary according to the lesion for which the operation was performed but quite apart from carcinoma or tuberculosis which by themselves may cause further complications or death the mere fact of diverting urine into the bowel can have profound physiological effects upon the patient. This fact has been appreciated for many years but it is only quite recently that the relationship between the mechanical and biochemical problems of the procedure has been revealed.

It is a common experience to find that some of those patients complain of anorexia, nausea, thirst loss of weight, and increasing lethargy though in all other respects they appear to be making good progress and may not show any rise in blood urea.

In 1950 Ferris and Odel found that nearly 80 per cent of a series of 141 uretero-colic anastomoses developed a high serum chloride and a low bicarbonate concentration i.e. a hyperchloræmic acidosis.

They thought that such a chemical imbalance could be due to two factors, namely renal tubular damage causing a loss of base in the urine, or selective reabsorption of chloride from the urine in the bowel. They also noted that if only one ureter was transplanted at a time, these blood changes did not occur until the second side was done. In one case acidosis was relieved by a temporary nephrostomy but recurred when the fistula was closed again. Furthermore they found that rectal incontinence reduced the degree of acidosis as did the use of an indwelling rectal tube. They therefore discounted the theory of renal damage and came to the conclusion that chloride was being reabsorbed from the urine in the colon. This reabsorption

they thought must be selective since the serum sodium level was not raised, nor was there any œdema

Doroshow (1951) came to similar conclusions but thought that tubular renal damage could not be excluded He considered that a combination of reabsorption of chloride and urea, a loss of base due to diarrhœa, and some degree of renal damage were probably all concerned.

Kekwick *et al* (1951) found that all five of their patients who exhibited this syndrome to a marked degree (four died), had hydronephroses, which they attributed to back pressure. They thought this pressure caused damage to the distal renal tubules, resulting in polyuria with dehydration and hyperchloræmic acidosis, but they admitted that some selective chloride reabsorption could not be excluded.

In 1951 Lapides carried out a series of observations and experiments to estimate the importance of renal damage in this syndrome. He observed that the patients who had electrolyte imbalance also had a history of attacks of pyelonephritis while one patient who showed the most marked chemical changes had proven renal damage before transplantation On the other hand, a small number of patients who were symptom free and had normal electrolytes had never suffered from any symptoms of pyelonephritis since operation. He also noted that over 75 per cent of cases showed abnormal pyelograms at some time or other after transplantation and that these changes tended to follow attacks of pyelonephritis and to be associated with periods of electrolyte disturbance.

He next took three normal patients with normal renal function tests and instilled their urine into their rectums for several days. The electrolytes and the blood urea levels remained normal. Similar experiments in three patients having poor renal function produced hyperchloræmic acidosis in two of them and a raised blood urea in all three, but recovery was complete when the instillations were stopped

Lapides concluded that after transplantation healthy kidneys were able to maintain a normal blood electrolyte balance by excreting the unwanted substances absorbed from the urine in the bowel, but that when the kidneys were damaged by infection or obstruction, or both, this mechanism failed and acidosis developed.

Wilkinson (1952) thought that the problem was one of potassium loss. The accumulation of urine above a continent sphincter stimulates an unusually great colonic secretion and perhaps hurried emptying of the lower ileum. This leads to a mild but repeated daily dehydration and loss of alkaline secretion, a state of slight but chronic water, potassium and bicarbonate depletion.

Stirling (Jacobs and Stirling 1952) concluded, from a study of the British Association of Urological Surgeons series, that if potassium deficiency was the chief cause it should be lowered in all cases but this was not so. He therefore considered that the low potassium was due to base loss by diarrhœa, and was a secondary phenomenon. He thought that selective reabsorption of chloride from the gut was probable, but that "the development of hyper chloræmic acidosis is largely dependent on the state of the kidneys."

It will be seen that at this stage the exact ætiology of the hyper chloræmic acidosis was uncertain since many people would not accept the fact of a differential absorption of sodium and chlorine from the bowel.

Differential Absorption of Chloride from Colon

This particular problem was investigated by Parsons and his colleagues (1952) and Pyrah (1954). Certain patients had an artificial bladder made from the isolated sigmoid colon and rectum into which one ureter was transplanted (Fig. 60). It was, therefore, possible to collect urine from the bladder and from the colon in the same patient. The volume of urine from the transplanted ureter in the bowel was slightly less than from the ureter in the bladder while the pH of colon urine was alkaline compared with the bladder urine, which was always acid. Although the colon urine had a lowered non protein content indicating some reabsorption of this substance, there was very little if any change in the potassium.

The most striking difference was the lowered sodium and chloride content of the colon urine, suggesting that both of these electrolytes were being reabsorbed in considerable quantities. Not only this, but it was obvious that more chloride was disappearing than sodium and, to prove that such a differential absorption did in fact occur from

the bowel into the blood stream, a series of brilliant experiments were carried out using radioactive ions of sodium and chlorine.

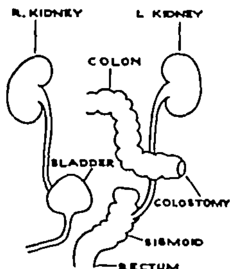


FIG. 60 First stage operation for total cystectomy using the distal colon as an artificial bladder (Reproduced by kind permission of the *Lancet* 1952, 2, 599)

Observations Using Radioactive Isotopes

Tracer amounts of ^{38}Cl and ^{24}Na were added to the urine in the bowel of patients having an artificial bladder of rectosigmoid.

The rate of absorption of the ions from the urine and their appearance in the blood stream was measured with Geiger counters. ^{38}Cl and ^{24}Na were used separately and simultaneously and could be differentiated by their dissimilar half-lives. Urine containing these isotopes was left in the bowel for up to 108 minutes The activity of the urine withdrawn from the bowel after 108 minutes showed that more chloride than sodium had been reabsorbed

The lower graph (Fig. 61) depicts the appearance of the two isotopes in the peripheral blood. The concentration of ^{38}Cl is approximately five times that of ^{24}Na.

During the same tests urine was collected from the bladder and Fig. 62 shows the excess of chloride over the sodium excreted during the experiment.

Even symptomless patients after uretero-intestinal anastomosis have their serum chloride levels raised to the upper limits of normal or above, but the onset of symptoms always appears to be associated

with a marked reduction in the carbon dioxide combining power and this may be more important as a cause of symptoms than the chloride level

The fact that the electrolyte disturbance may only develop months or years after transplantation would indicate that the reabsorption

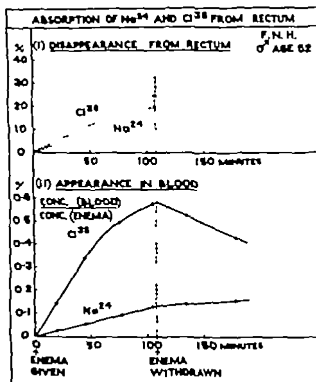


FIG. 61 Differential absorption of sodium and chloride. (Pyrah, L. N., *Brit J Urol*., 1952, 24, 317)

from the bowel is not the whole picture, and Parsons and his colleagues agree with other workers that renal impairment as well as reabsorption is necessary before symptoms develop

Unfortunately renal damage occurs eventually in practically all of these patients, so that the ultimate prognosis is bad even when their carcinomas etc. have been cured. It is this fact which is driving urologists to seek some other way of diverting the urine from the kidneys, hence the renewed interest in artificial bladders made from

small intestinal loops where infection and the degree of absorption can be controlled.

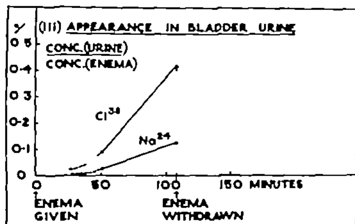


FIG. 62. Graph showing excess of chloride over sodium excreted during the experiments of differential absorption. (Pyrah, L. N., *Brit J Urol.*, 1952, 24, 312.)

Treatment of Electrolyte Imbalance

Post-operatively it is important to avoid large quantities of urine in the bowel, hence the importance of a freely draining rectal tube. The old idea of pushing intravenous saline in the presence of *oliguria* is to be condemned. The patient requires just sufficient to make up for his losses by lungs, kidneys, skin and alimentary tract, while an excess of salt is the last thing he usually needs

In the presence of *polyuria* the serum electrolytes must be carefully observed because chemical replacement will probably be necessary Pyrah (1954) recommends that sodium lactate should be added to the sodium chloride for intravenous use, so that the ratio of sodium to chloride is 1·4 to 1 in order to overcome the differential absorption factor He also gives three grammes of potassium daily and as soon as oral feeding starts the patient is given a mixture of 4 G sod. bic., and 4 G potassium bicarbonate in twenty-four hours.

Even in the absence of symptoms it is most important that these patients should be followed up when they leave hospital and that their general practitioner should be acquainted with the clinical syndrome of electrolyte imbalance (Tables 2 and 3).

TABLE 1 *Normal Electrolyte Values* (Pyrah 1954)

Hæmatocrit	40–47
Plasma proteins, gm. per 100 ml	6 5–7 5
Chloride, NaCl mgm. per 100 ml. mEq./l	560–620 96–106
CO_2, c.p vols. per 100 ml. mEq./l	55–70 24 8–31 5
Sodium, mgm. per 100 ml. mEq./l	305–325 132–141
Potassium, mgm. per 100 ml mEq./l	16–20 4 1–5 1
Potassium, R.B C. mgm. per 100 ml. mEq./l	372–400 95–102
Urea, N_2 mgm. per 100 ml.	10–20
Phosphorus, mgm. per 100 ml. mEq./l	2–4 1 16–2 32

TABLE 2

Blood Electrolyte Levels in Two Patients who are without Symptoms The first Case shows a Hyperchloræmic Acidosis and the second shows Top Normal Chloride Levels (Pyrah, 1954 *Ann Roy Coll Surg Eng.*, 14 191)

Patient Age at Operation and Sex	Month, P O Tech-nique	CO_2 c p m Eq./l. vols./100 ml.	Cl m.Eq./l. NaCl mgm./100 ml	Na m Eq./l. mgm./100 ml	K m.Eq./l. mgm./100 ml	B.U N — mgm./100 ml	Diagnosis
Normals	—	24 8–31 5 55–70	96–106 560–620	132–141 305–325	4 1–5 1 16–20	— 10–20	—
R. H., 41 male	60 Coffey	19 7 43 3	114 669	137 316	3 8 14 9	29	Bladder Neoplasm
D. R., 3, female	66 Coffey	26 9 59 7	106 420	133 318	4 05 15 7	16	Bladder extrophy

TABLE 3

The Findings of another Group of Patients with Symptoms of Electrolyte Imbalance all of them showing an Acidosis and three of them a Hyperchloraemia (Pyrah, 1954 *Ann Roy Coll Surg., Eng.*, 14 191)

Patient / Age at Operation and Sex	Months, P.O Technique	CO_2 c.p m.Eq./l. Vols /100 ml.	Cl m.Eq./l. NaCl mgm./100 ml.	B.U.N — mgm./100 ml	Diagnosis
Normals	—	24 8–31 8 55–70	96–106 560–620	— 10–20	—
F P., 64 male	12 Nesbit	18·4 34 2	113 661	41 2	Bladder neoplasm
E. W 47 male	3 Nesbit	21 1 46 9	96 560	36	Bladder neoplasm
A. J 40 female	1 Leadbetter	22 1 49 1	116 679	16 8	Vesico-vaginal fistula
N. R. B 53 male	12 Nesbit	17·5 38 9	105 614	56 1	Bladder neoplasm
O M., 51 female	17 Nesbit	22 2 49 3	124 724	59·4	Bladder neoplasm

A high fluid intake should be encouraged and salt, other than that used in cooking, should be forbidden Four grammes of sodium bicarbonate should be given daily while the urine from the bowel should be evacuated as often as possible. I have known patients boast of being able to hold urine in their rectum for eight to ten hours but this must be wholeheartedly condemned.

The treatment of patients who develop mild symptoms of hyperchloremic acidosis is simple enough in the early stages, and consists of withholding salt and administering sodium bicarbonate. If the patient is already severely dehydrated nauseated and lethargic, hospitalisation is generally necessary in order to correct the electrolyte imbalance. Even patients in coma may recover completely with correct treatment.

ARTIFICIAL BLADDERS

The long term results of any large series of uretero-colic anastomoses are so unsatisfactory that urologists are turning their attention to other methods of urinary diversion.

In order to overcome the present difficulties artificial bladders are being made from intestinal loops, which are isolated from the main fæcal stream Such measures reduce not only the chances of infection but also the absorptive area exposed to the urine.

The idea of a separate artificial bladder is not new and was originally conceived as long ago as the early work on uretero-colic anastomoses as we know it today However the desire to render the patient continent by use of the anal sphincter rather than having a fistula on the abdominal wall accounted for its disfavour Today we are returning to the old ideas on the grounds that a certain amount of permanent inconvenience *from an abdominal fistula may* be a small price to pay for a live healthy patient

The ideal procedure would be one where an artificial bladder could be joined on to the normal sphincter mechanism Rubin (1951) working with dogs, transplanted the ureters into an isolated sigmoid loop which he then joined to the remains of the bladder neck. The continuity of the bowel was restored and, although this was all done in one stage, the results were satisfactory and encouraging He reported success with this operation in one human patient but gives no further details.

Levitsky (1953) divided the sigmoid at the level of the rectal ampulla and closed both ends. Using blunt dissection, he passed the upper sigmoid stump down behind the rectum as far as the coccyx and internal rectal sphincter The anal sphincter was then held open with retractors from below and, through a transverse incision in the posterior rectal wall above the sphincter the stump of sigmoid was pulled down and left projecting through the anus where it was held with a few catgut sutures. At a second operation, the bladder and uterus, etc., were removed and the ureters transplanted into the isolated rectal ampulla. By this means the anal sphincter was made to control both urine and fæces although they were separated from each other No long-term results are available.

Isolated Rectum and Sigmoid Colon

The use of the isolated rectum and sigmoid as an artificial bladder in the human being is not new and has been reviewed by Glaser (1952) and Pyrah (1954) In these cases the rectal sphincter will

provide adequate control of the urine, but the patient has a permanent end colostomy Pyrah found that patients treated by this means showed no clinical evidence of ascending renal infection although there was moderate but easily controlled electrolyte upset in some cases. He also raised the question of whether a colostomy is not a reasonable price to pay for a healthy patient, and concludes that these clinically are among the best results of my series of cases of transplantation of the ureters.

However the use of existing sphincter mechanisms causes further complications in many cases and may not overcome the back pressure problems. For this reason much recent work has been carried out using artificial bladders with simple fistulous openings on to the skin

Isolated Ileocæcal Loops

Where the rectal sphincter mechanism is still intact, as in the majority of urological cases, it is possible to restore continuity of *the bowel after isolating the " bladder loop so that only one* fistula has to be controlled. The ileocæcal region has been used in such cases by Bricker (1950) Gilchrist *et al* (1950) Merricks *et al* (1951), Peck and Newland (1952) Glaser (1952) and Moore (1953), and in general all these authors report favourably on their results

The underlying attraction of this procedure was the hope that if the ileal stump was used to form the skin fistula, the ileocæcal valve *would provide a reasonable degree of continence up to an optimum* capacity To a certain extent this is so, and emptying has to be achieved by catheterisation. One serious disadvantage of the method is the need for such care and regularity over this catheterisation, since all authors are agreed that if pressure is allowed to build up in the cæcum the risks of infection absorption and back pressure are great. *In practice the benefits derived from the sphincter action of the ileocæcal valve are outweighed by its disadvantages*, since a bag has to be worn in most cases anyhow

Avoidance of a Wet Colostomy

In certain conditions the whole pelvic viscera, including the rectum and bladder may have to be excised If the ureters are

transplanted into the colon a wet colostomy results and is very difficult to control

Bricker (1950 1952) has recorded a large series of pelvic evisceration cases requiring a terminal colostomy in which he transplanted the ureters into various isolated intestinal loops draining on to the abdominal wall and relied entirely on a Rutzen bag to keep the patient dry These cases, therefore, had two fistulous openings one fæcal and one urinary rather than one wet colostomy In his more recent cases he has used the terminal ileum rather than the ileocæcal region or the sigmoid for his artificial bladder and when allowance is made for the morbidity and mortality due to the very extensive primary pathology in these patients the immediate and late post-operative results of the urinary diversion alone appear to have been very gratifying

Of fifty five ureters so transplanted thirty nine showed normal or only minimal dilatation six months after operation while only one case (bilateral hydronephroses) showed any hyperchloræmic acidosis

Isolated Ileal Loops

The use of the ileum for the artificial bladder has been gaining in popularity and, quite apart from Bricker s work (1952) referred to previously Wells (1953) and Annis Hunter and Wells (1953 1954) have all reported favourably on this procedure, of which they have now had considerable experience.

The steps in the formation of an ileal loop bladder are described by Wells (1953) but are still being modified. Following the careful exposure of the ureters, the lower ileum is drawn out of the abdomen and a piece twelve inches long is selected about eight inches above the ileocæcal valve. After isolation of this segment, ileal continuity is restored by end-to-end anastomosis above and in front of the urinary loop The divided end of the left ureter is drawn through the meso-sigmoid and split longitudinally for three-quarters of an inch, after which it is anastomosed to the open proximal end of the urinary loop The right ureter is similarly split and anastomosed to a transverse incision on the antimesenteric border of the ileum at the pelvic brim. The ileal loop is fixed to the pelvic brim and the distal

open end is drawn through a stab wound on the spino-umbilical line, care being taken to close all gaps and gutters which might lead to internal herniation The ileum projects for an inch or more, the mucosa being folded back and sutured to the skin in order to form a spout. Urine is collected by a disposable bag rather than by an indwelling tube which may lead to ulceration.

Some patients cannot tolerate an adhesive bag, and Hunter (Annis, Hunter and Wells, 1954) has fashioned a spout ileostomy in these cases. This should be at least two inches long and is made to curl downwards by covering the upper surface with a full thickness skin graft and the lower surface with a split skin graft, which subsequently contracts. By day the spout drips into a non-adhesive collecting bag, but leakage at night may occur

After-care

The after-care in such cases is much simpler than in uretero-colic anastomosis although the tendency to ileus development should be countered by reducing the oral fluids as much as possible for several days relying chiefly on intravenous infusions. Control of the blood chemistry is essential during this period but, once normal feeding and drinking has commenced, no serious electrolyte imbalance should occur All workers are agreed that the late risks of acidosis and hyperchloræmia are greatly reduced with this procedure, although electrolyte imbalance can occur as recorded by Wilson (1953)

Ureteric Replacement by Ileal Loop

Annis (1953) has shown by his animal experimental work that life can be satisfactorily maintained on a single kidney connected to the bladder by a loop of ileum. The bridging of large defects in the human ureter by similar means is also reported by Longuet (1948), Aboulker (1950) Baum (1954) and others, so that the suitability of ileum as a urinary channel is well established.

Foret and Heusghem (1953) have reported a case in which there had been stenosis at both uretero-vesical orifices resulting in bilateral hydro-ureters. They isolated a 50 cm. length of ileum and made of it a U loop The base of the U was anastomosed to the bladder while the two limbs were used to replace the pelvic and iliac portions

of the ureters. A year later the renal function had improved and no serious electrolyte disturbance was noted.

Theoretically there is the risk of reabsorption from the ileal

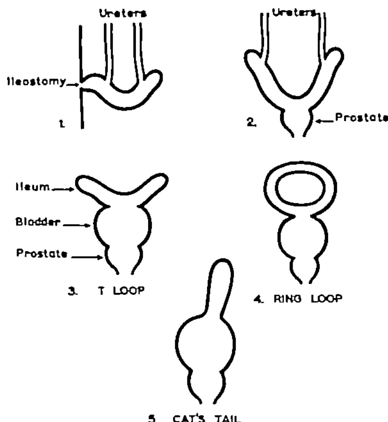


FIG. 63 Various methods of utilising the ileum in urology

(1) Uretero-ileostomy
(2) Complete replacement of bladder by a loop of ileum anastomosed on to the prostatic capsule.
(3) "T" loop ileocystoplasty
(4) Ring loop ileocystoplasty
(5) "Cat s tail" ileocystoplasty to avoid a blind terminal end.

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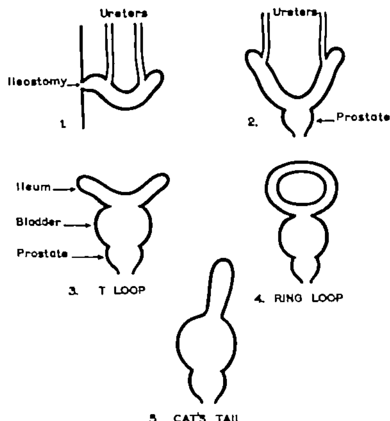


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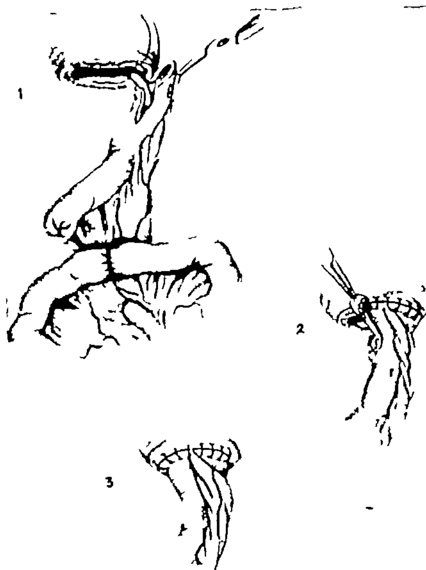


FIG. 64 "Cat's tail" ileocystoplasty
A blind terminal end of ileum can be avoided by this means.

to failure, while some of the unpublished results obtained by British urologists so far have not always been as satisfactory as the case

It will be noted that the references quoted in this section are all very recent and it will be several years before a true assessment can be made of the value or otherwise of intestinal loops in urology (Fig. 63)

Ileo-cystoplasty

The immediate results of uretero-colic anastomosis in cases of contracted bladder cannot be considered satisfactory when the *British Association of Urological Surgeons Review* (Jacobs and Stirling, 1952) reveals an operative mortality of 13·0 per cent, whether done for a tuberculous or for a non tuberculous chronic interstitial cystitis. The survival rate, though better than the carcinoma cases, shows that only about 55 per cent of the patients were alive after five years

And yet all urologists are agreed that some surgical intervention is called for when the bladder capacity is reduced to two to three ounces so that frequency amounts almost to incontinence. In an endeavour to avoid the problems of renal failure and hyperchloræmic acidosis further attempts have been made recently to enlarge the urinary bladder rather than divert the urinary stream.

Couvelaire (1950) reported a case of a chronic tuberculous contracted bladder in which he anastomosed an isolated loop of ileum on to the bladder with very gratifying results

Cibert (1953) has recorded eighteen cases of ileo-cystoplasty and describes one of his tuberculous cases in detail The bladder was exposed deep down in the retropubic space, and freed as much as possible from the surrounding adhesions Through a four-inch transverse incision in the peritoneum just above the bladder a loop of ileum was delivered isolated and closed at both ends, after which it was anastomosed to a transverse opening in the dome of the bladder The peritoneal opening was closed, thus making the bladder loop extra peritoneal. The bladder wall was grossly thickened and the mucosa was difficult to define. Cibert considers that the results in his eighteen patients amply justify the operation which he considers to be much more suited to these cases than uretero-colic or uretero-cutaneous anastomosis. It must be realised that such an operation in the presence of active tuberculosis is practically doomed

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reported in detail by Cibert. However there is no doubt that more and more conservative and reparable surgery is becoming possible as our knowledge of the antibiotic control of tuberculosis extends, and many cases of ileo-cystoplasty for tuberculosis or interstitial cystitis have been recorded (Annis, Hunter and Wells, 1954 Annis, 1956 Pyrah, 1954 1956 Jacobs, 1955 Hanley 1956)

British surgeons are finding that the relief afforded by ileo-cystoplasty to cases of interstitial cystitis as opposed to tuberculous cases may only last for about six to nine months, after which time symptoms return. This appears to be due to extension of the ulceration into what is left of the original bladder This has occurred in one of the author s cases even after an extensive partial cystectomy at the time of the ileo-cystoplasty

In the performance of an ileo-cystoplasty a T shaped approximation should be avoided if possible, since it has been shown that the blind distal loop does not empty as efficiently as the proximal loop and that it tends to collect mucous (Hanley 1956).

Fig. 64 shows one of the author s cases of interstitial cystitis where the distal end of the loop was joined to the remainder of the bladder after an extensive partial cystectomy This form of "cat s tail" anastomosis avoids any blind end and appears to function more satisfactorily but complete emptying of the bladder during one act of micturition is a rarity and much work requires to be done on this problem.

Tasker (1953) has described a technique whereby a loop of ileum is opened out and applied as a patch to the bladder and there are an increasing number of private reports showing that such a procedure is very useful for example when an extensive partial cystectomy has been performed Jacobs (1955) reports favourably upon this technique for a case of interstitial cystitis, and such a procedure may well supersede the ordinary loop anastomosis.

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CHAPTER 11

URINARY LITHIASIS

We know that the incidence of calculi is greater in peoples living on a diet with a low vitamin content, or in climates where excessive dehydration occurs. We know that urinary stasis due to mechanical obstruction or to recumbency favours urinary infection, which in turn favours stone formation However these simple facts have occupied the literature for the last twenty years or more and although the incidence of urinary calculi in this country has been greatly reduced the credit must go to the improved hygiene and dietary standards of the country as a whole rather than to advances in urology and we are still left with the hard core of calculus patients in whom the above causes can be excluded

The number of known and accepted different factors concerned with the broad problems of urinary lithiasis shows that no single one of them constitutes the initial trigger mechanism, and since the individual calculi may differ completely in their chemical and other compositions this is perhaps not surprising.

Certain metabolic disturbances lead to the excretion of salts in abnormal forms and quantities with resultant urinary stone formation.

Cystinuria has always been quoted as a classical example of an inborn error of metabolism but recent work (Dent and Rose, 1951 Dent, Heathcote and Joron, 1954 Dent, Senior and Walshe, 1954) would indicate that cystine appears in the urine not because there is a failure in cystine catabolism, but because the kidneys allow it to escape. In fact cystinuria is not a metabolic disorder in the old accepted sense Dent and his colleagues have shown that cystinuria is a genetically determined defect in the renal tubules in which there is a failure to reabsorb cystine or certain other amino-acids such as lysine, arginine or ornithine

Cystine crystals are soluble in an alkaline urine but may be deposited as waxy yellow calculi in an acid medium. However the

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Cystine crystals are soluble in an alkaline urine, but may be deposited as waxy yellow calculi in an acid medium. However the

amount of cystine present in the urine is probably of greater importance than the pH Many people may possess this genetically conferred defect of tubular reabsorption in a minor degree and will not form stones However if a child inherits the responsible genes from both parents, it may excrete cystine in large amounts and will then form cystine calculi It has been shown that cystine stones only form in patients who excrete cystine in large amounts (Harris and Warren 1953) and this is perhaps the only example which can be quoted to show that the probability of actual stone formation bears any direct relationship to the amount of stone forming substance contained in the urine.

This whole problem has been very fully reviewed by Dent and Senior (1955) who have shown that in the cystinuric patient the total daily excretion of cystine can be held in solution by about three litres of urine at pH 6 Although the solubility is increased in an alkaline medium the pH must be over 7·6 before any appreciable difference is noted, and since such a pH is impossible to maintain for long periods, it is doubtful whether alkalisation of the urine is of any value as a prophylactic measure. Dent also points out that the day urine mav be undersaturated with cystine, while the night is supersaturated and that stone formation probably occurs at night.

A long-term research project is in progress whereby the fluid output is so increased throughout the twenty four hours that under saturation can be maintained at all times. Under such conditions stones cannot form while existing deposits will probably be dissolved The results so far are encouraging.

Various other pathological conditions cause the excretion of abnormal amounts of different salts and include bone decalcification associated with recumbency or with hyperparathyroidism. However in spite of the great increase of calcium and phosphorus in the urines of these patients calculus formation is not universal and some other mechanism appears to be necessary

Hyperparathyroidism

Parathyroid hyperplasia or adenoma formation producing the classical picture of radiological bone changes, spontaneous fractures, and renal calculi or nephro-calcinosis, is unlikely to be missed. Of

much greater importance to the urologist is the patient suffering from hyperparathyroidism without bone changes but who develops recurrent renal calculi due to hypercalcuria The condition will not be diagnosed in such cases unless special steps are taken to confirm its presence. Attention was drawn to this problem by Castleman and Mallory (1935) and later by Norris (1947) who collected seventeen cases Several more were recorded by Miller and Mitchell in 1952, bringing the total up to twenty-five at that time. However recent publications by Hellstrom (1955) and Pyrah and his colleagues (1955) show that hyperparathyroidism is much commoner than we previously realised and that there is little excuse for failing to exclude this condition, certainly in cases of bilateral or recurrent calculi, if not in all lithiasis patients.

Blood and Urine Changes

There is an excessive loss of phosphorus from the blood-serum into the urine. The drop in serum phosphorus causes a rise of serum calcium, which is obtained from the bones and is subsequently excreted in the urine. The normal serum calcium level in a fasting state is 10 mgm. per 100 ml and Cook and Keating (1945) consider that if this figure is increased by 1 mgm. on repeated estimations it is diagnostic of hyperparathyroidism. The serum phosphorus level is much less constant from day to day the average being 3 5 mgm. per 100 ml., but if the average drops below 3·0 mgm per 100 ml it is highly suspicious of hyperparathyroidism. However it should be noted that Albright, Aub and Bauer (1934) reported a case of hyperparathyroidism with a raised serum phosphorus because renal failure prevented the excretion of phosphates in the urine.

The true incidence of renal calculi in hyperparathyroidism is unknown since only a relatively small number of patients are fully investigated, but Miller and Mitchell (1952) summarised the literature as follows

42 out of 83 (51 per cent) (Albright, Baird and Cope, 1934)
118 „ „ 322 (37 per cent) (Norris, 1947)
30 „ „ 36 (84 per cent) (Chute, 1939)
47 „ „ 67 (70 per cent) (Cope, 1942)
14 „ „ 18 (78 per cent) (Cook and Keating, 1945).

It is important to realise (Albright Baird Cope and Blookberg, 1943) that radiological bone changes are late signs in the disease and Cope (1942) considers that up to 15 per cent of all renal calculi cases will eventually show clinical hyperparathyroidism

Diagnosis

It is obvious that a large number of lithiasis cases associated with hyperparathyroidism will pass unnoticed unless the latter disease is deliberately excluded, a fact which is emphasised by Miller and Mitchell s claim in 1952 that their patient is the only case reported in which there has been no operation for calculi prior to arriving at the diagnosis of hyperparathyroidism. In the absence of bone changes it may be difficult to establish the diagnosis, and this means that the urologist must have the condition constantly in mind particularly when dealing with recurrent or bilateral stones. In most cases estimations of the serum calcium prove diagnostic. Taking the upper limit of normal as 11 mgm. per 100 ml. values ranging up to 23 mgm have been recorded. However the detection of the less advanced cases is of greater importance to the urologist, and when in doubt more careful estimations are essential. Such estimations are by no means simple to carry out and may in fact be valueless unless the controlled basal conditions of a metabolic unit are available. The patient has to remain in the unit for five to seven days, on a carefully controlled neutral ash diet containing a known daily calcium content At the end of this time, three successive total 24-hour urines are analysed for calcium Normal ambulant patients under these conditions excrete up to 100 mgm. calcium per day Figures of 150 mgm. are suggestively high, and over 200 mgm are consistent with a diagnosis of hyperparathyroidism.

Cook and Keating (1945) stress the importance of repeated estimations under basal conditions. They also consider that a rise of 1 mgm above the normal blood-calcium level of 10·0 mgm. per 100 ml. is diagnostic if this level is maintained.

As stated previously the serum phosphorus may vary in different people or even from day to day in the same person. The normal level is 3 5 mgm. per 100 ml. but if the average of several estimations

is below 3 mgm per 100 ml hyperparathyroidism should be suspected

Treatment consists in partial resection of a glandular hypertrophy or removal of an adenoma when present The small tumours may be very difficult to find Chute (1939) records that in a collected series of thirty six patients six of them had undergone one or more previously unsuccessful operations before the adenoma was found, while similar multiple operations are reported by Pyrah (1955) and by Hellstrom (1955)

Unless the calculi are causing serious obstruction, the parathyroid surgery should be completed first of all, because some of the calculi will subsequently disappear spontaneously Pyrah (1949) records three such cases where the stones consisted of pure calcium phosphate.

Theories of Stone Formation

The mere presence in the urine of all of the chemical components of a calculus, even in excess or in association with stasis and infection does not necessarily lead to the actual formation of a stone. Butt (1952) and his colleagues have confirmed previous theories that the urinary salts will come out of solution and form solid crystals if the balance of the protective colloids is disturbed. But even when actual crystals form there is no explanation as to why they join together to form a calculus rather than escape down the ureter as small crystals. It is therefore obvious that the mass of data which is accumulating round the problem of urinary lithiasis is largely marking time until we can discover what actually occurs at the moment when the dissolved substances come out of solution and form a solid nucleus, and also where this takes place.

"Randall s Plaques

Randall (1937) postulated that whenever or for whatever reason a nucleus forms it must surely be washed down the ureter whilst still microscopically small unless it is held up somewhere, thus enabling a large chemical incrustation to take place.

Putting this theory to the test, he examined hundreds of post mortem normal kidneys with a hand lens, and in many cases found numerous *small plaques* of calcium deposited in the interstitial

tissue at the tips of the renal papillæ These plaques were not in the tubular system. He considered that if the thin overlying membrane became eroded thus allowing the urine to come into contact with the calcium plaque, deposition of salts would occur until the mass was large enough to break off as an actual calculus. The presence of Randall's plaques has since been confirmed by several workers, including Vermooten (1942) who considered that the calcium was deposited in the collagen fibres of the basement membrane of the tubules, or of the blood-vessels, as well as in the interstitial tissues.

Microliths

In 1946 Anderson and Macdonald examined a large series of kidneys, normal and otherwise, and found microscopic calculi scattered throughout the parenchyma of every specimen. They defined their microliths as a deposit of calcarious material in the substance of the kidney of a size sufficient to be seen easily under the ordinary low power microscope lens and the diameter is at least five or six times that of a normal tubular cell. They considered that these microliths were particles of calcium inside macrophage cells which had clumped together forming microscopic calculi. Since they found them in all kidneys of patients over nine years old, they thought that Randall's plaques were also minute calculi of similar nature, rather than actual lesions in the structure of the renal papillæ. However they agreed that once the microlith came into contact with the urine by ulceration of its overlying membrane, a true stone could then form by the usual process

Lymphatic Theory

It will be seen that Randall's plaques and Anderson's microliths are accepted facts, although their true nature is in dispute Carr (1954) has produced a completely new theory which accounts for all types of calcium deposition and is worthy of much future investigation. He has developed methods of radiological examination of kidneys exposed at operation of portions of kidneys removed after partial nephrectomy for calculus, and of large numbers of routine post mortem specimens

Briefly the technique consists of taking a series of exposures (up

to fifty in some cases, using a fine focus tube slow films and low voltage) of progressive slices of kidney each of which is examined with a hand lens to compare the clinical and radiological appear ances As the slices become thinner special apparatus is required, but the films are of such fine grain that they can be examined under the microscope so that magnifications of up to 300 times can be obtained.

This technique of *microradiography* has far reaching possibilities,

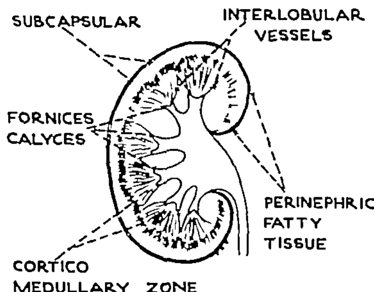


FIG. 65 Drawing of a slice of kidney to illustrate the position in which concretions are most commonly found. (Carr 1954 *Brit J Urol.*)

and Carr found that concretions of the size of 0 5 mm were easily detectable, whereas by the ordinary histological means such bodies would drop out of the sections on the microtone, or would be washed out during the staining and fixing. This work is still in progress, but several important conclusions have already been published.

Using microradiography practically all kidneys from patients over nine years old show opacities large enough to be visible to the naked eye. A normal kidney contains one or two but some contain a

dozen or more Carr calls these *concretions* in order to distinguish them from (*a*) microliths, defined by Anderson as being visible only under a low power microscope and (*b*) *true renal calculi* a term which he considers should be reserved for bodies situated actually within the calyces or pelvis.



FIG 66. A microradiograph of a "linear opacity" showing that it is composed of multiple small bodies. (Carr 1954 *Brit J Urol*)

These concretions tend to lie in well-defined positions (Fig. 65) namely (1) Just outside the fornices of the calyces or in line with them along the paths of the intralobular vessels, at the sides of and between the pyramids (2) in the corticomedullary zone (3) immediately beneath the capsule With the exception of those under the capsule, concretions are always in close proximity to vessels, but are always just outside them.

When a microradiograph is taken of one of the linear opacities so continually seen in renal X rays, it is found to consist of a chain of separate opacities (Fig 66) When a concretion is found in a papilla it may be of considerable size without having reached the surface of the papilla. Collections of these concretions occur just

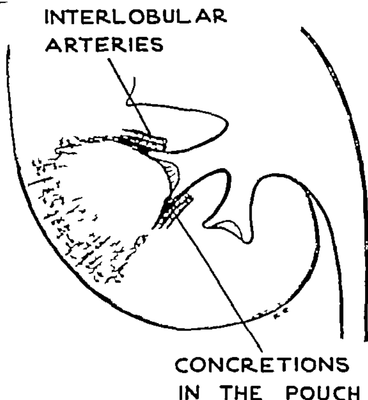


FIG. 67 Drawing showing concretions lying just outside the fornix of a minor calyx. (Carr 1954 *Brit J Urol*)

outside both the arteries and veins (Fig. 67) Carr considers that these concretions develop inside the lymphatics of the kidney which have recently been studied by Rawson (1949)

If as seems probable, Anderson s microliths and Randall s plaques are normal findings, then we must accept the fact that precipitation of salts in the renal substance is a normal process. Carr s lymphatic

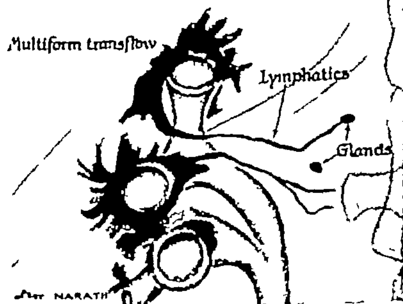


FIG. 68 Radiograph and explanatory drawing of pyelolymphatic backflow from the fornices of the calyces. (Carr 1954 *Brit J Urol.*)

theory fits in with the above views and also accounts for the means whereby normally these concretions are conveyed away from the kidney to the lumbar nodes without causing true renal calculi much in the same way that foreign bodies are removed from the alveoli of the lungs into the mediastinal lymph nodes. This channel can some times be demonstrated by pyelolymphatic back flow (Fig. 68) If the efferent lymphatics become blocked by inflammation or fibrosis, or if the concretions form too rapidly to be removed, such as may occur in hyperparathyroidism or decubitus states then the con cretions will agglomerate and finally rupture through into the calyces and form true calculi

Carr s work is a further important addition to our knowledge of *how* deposits of solid material grow into renal calculi but we still have to find out *why* such deposits occur

Treatment of Urinary Lithiasis

There have been few recent advances in the treatment of this condition, although certain general surgical principles have been re emphasised. For example removal of a calculus anywhere in the urinary tract must be accompanied by the correction of any obstruc tive factor since obstruction and incomplete removal are the two chief causes of recurrence Complete removal of the minute fragments frequently accompanying a large calculus may be difficult or more likely impossible, and because an excessive number of Randall s plaques, Anderson s microliths and Carr s concretions are found in relation to a damaged calyx containing a calculus, the performance of a partial nephrectomy is based upon very sound principles, especially when the stones are in the lowest calyx (page 81) Hanley (1950) Stewart (1953 1955)

During a simple pyelolithotomy the problem of the small fragment which breaks off and falls into a calyx may be very serious Various methods of overcoming this difficulty have been described. The pelvis can be filled with a jelly like substance which it is hoped will set round the particles thus incorporating them in the resultant "cast" which can then be withdrawn in one piece. Forcible irrigation of the pelvis and calyces with saline may help but the

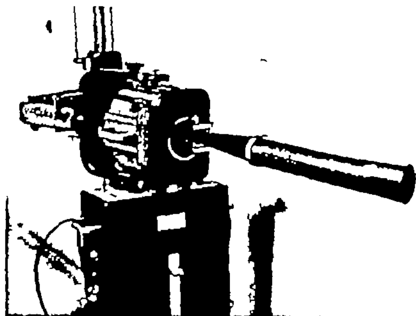


FIG 69 Westinghouse tubehead with special cone and special applicator fitted on the cone. The applicator can be taken off and boiled and can be rotated on its cone. The tubehead can be raised and lowered and tilted. (Nicholson, 1949 *Brit J Urol.*)

FIG 70. The open frame and perspex screen are lying to the right. The screen is placed in the frame which closes with a snap. The reflecting mirror which is ball jointed to the basal pillar can be angled in any direction. (Nicholson, 1949 *Brit J Urol.*)

only way of being reasonably sure that no particles remain is to X ray the kidney *in situ* before completing the operation This necessitates having a portable X ray apparatus in the theatre but there is little excuse for performing a nephrolithotomy without such precautions.

An ingenious method of using a small fluorescent screen during the actual surgical exposure has been devised by Nicholson (1949) The X ray tube head is fitted with a long portable cone which is applied directly to the exposed kidney A special fluorescent screen is applied to the opposite side of the kidney and by means of a mirror the surgeon can visualise the kidney substance and remove calculi under screen control (Figs. 69 and 70)

Stone-dissolving Solutions

Although it is a simple procedure to dissolve a urinary calculus in a test tube it is quite another matter to do so in the renal tract Phosphatic deposits are soluble in an acid solution and provided there is no organic nucleus, a pure phosphatic urinary calculus should be easily dissolved by such means Great claims were made for Suby s G solution in this respect (Suby 1943 1944) * but in practice such large volumes of the buffered solution have to be brought into contact with the calculus that the method is rarely applicable The original attempts to effect dissolution by ureteric catheter irrigation have been largely abandoned in this country and while marked reduction in the size of a calculus can often be achieved by irrigation through a nephrostomy tube complete dissolution of the stone is very rare.

However G solution is very valuable for washout purposes in cases of phosphatic cystitis (Abramson 1943) and it is also useful in preventing phosphatic encrustation on nephrostomy tubes, etc although the introduction of non water wettable plastic catheters has reduced this problem in any event.

Suby s G" solution

Citric acid monohydrate	3 35 G
Magnesium oxide anhydrous	3 84 G
Sod carbonate anhydrous	4 37 G
Water to 1 000 ml.	

Prevention of Recurrence of Urinary Calculi

Hyaluronidase and Urinary Lithiasis

Butt and his colleagues (1952) stated that the development of calculi could be prevented if a high level of protective colloid could be maintained in the urine They suggested that the injection of hyaluronidase resulted in the excretion of hyaluronic acid (or some other breakdown products) in the urine, and that the surface tension was lowered as a result. They also noted that in calculous patients who had a turbid urine the injection of hyaluronidase resulted in a clearing of the turbidity and they based their dosage on turbidity-reducing units.

They also stressed the fact that unless sufficient hyaluronidase is administered the opposite effect may occur and the urine may become more favourable for the formation of calculi This danger and the fact that the treatment can only be administered by daily subcutaneous injections over prolonged periods, if not for life, has prevented its extensive trial in this country In fact the only British reports available do not support either the theories or the claims of Butt and his colleagues For example Smiddy (1954) failed to show that hyaluronidase injections had any effect on urinary surface tension, while he thought that hyaluronidase, far from retarding stone formation, actually enhances the production of magnesium ammonium phosphate hexahydrate in the rat. In a small clinical trial Dingley and Badenoch (1954) concluded that hyaluronidase has no material effect upon the natural history of stone formation, a fact which can be amply supported by the author (Hanley 1954).

Aspirin and Urinary Lithiasis

A different approach to the prevention of recurrence of calcium-containing stones would be to prevent supersaturation of the urine with the stone forming salts. Prien and Walker (1955) have drawn attention to the fact that the solubility of calcium phosphate is greatly increased by the presence of glucuronosides in the urine, and that this can be achieved by the administration of salicylic acid derivatives such as acetylsalicylic acid.

Prien found that aspirin 2 G daily in divided doses was effective

and relatively non toxic. Nineteen patients with a recurrent stone history were treated for twelve to eighteen months, and it was found that there was no increase in size or new stone formation in seventeen patients during this time.

This regime has not been confirmed in this country

Aluminium Gels

Short and Carter (1949) have approached the problem of recurrent calculi by attempting to limit the amount of phosphorus available for absorption from the gut.

They gave aluminium hydroxide in order to produce insoluble aluminium phosphate salts in the bowel and reported that the urinary phosphate excretion was thereby reduced

Although the results in twenty-two patients were encouraging no further large-scale tests have been reported.

It will be seen that major recent advances in the prevention of formation or recurrence of calculi are understandably absent. This is chiefly because it is impossible to claim that by using any special technique or therapy one has prevented the formation of a stone, which might not have developed in any case. Butt s work on hyaluronidase, aluminium gels and aspirin, though interesting in itself has suffered from this criticism

However recurrence of calculi in cases of hyperparathyroidism can be prevented by removal of the offending adenoma, but in all other instances vague generalisations form the basis of after treat ment. A very full urological investigation is necessary in all cases, while the stone itself must be analysed chemically

If cystinuria is present sodium bicarbonate and an alkaline-ash diet may be prescribed, since the crystals are soluble in an alkaline urine However this is largely theoretical since a pH high enough to affect solubility cannot be maintained for long periods, let alone permanently The only really useful therapy is to raise the daily fluid intake to such a level that the urine is permanently under saturated with cystine throughout the twenty-four hours. This must be kept up indefinitely

Uric acid stones or crystals calls for a low purine diet and alka lanisation of the urine Various special diets have been devised for

the different types of calculi but although popular in America, they have not been widely used in this country (Higgins, 1943 Flocks, 1950)

Even when all the above precautions have been taken the most important factors in stone prevention are the elimination of obstruction and urinary infection the provision of a balanced diet containing adequate vitamin supplies (A and B_1 chiefly) and the establishment of a large daily fluid intake

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CHAPTER 12

GENITO-URINARY TUBERCULOSIS

In spite of the fact that for many years students have been taught to regard genito-urinary tuberculosis as a local manifestation of a generalised disease, this has been merely a *cliché* and far too often the standard treatment has been, and unfortunately still is, a nephrectomy or an orchidectomy with little or no thought for the pulmonary or other systems involved or for the natural course of the disease.

From out of a mass of conflicting theories David Band's (1943) work and review emerged as a classic and most urologists now consider that, during the early stage of a primary focus, a tuberculous bacillæmia may occur and produce lesions elsewhere in the body depending on the virulence of the attack and the resistance of the host Both kidneys most certainly develop small multiple cortical lesions in this initial phase though happily the majority of these heal or are successfully walled off

It is probable that such lesions are much more common than reported and that they account for the transitory tuberculous bacilluria recorded, in varying frequency by different workers in the early stages of pulmonary and bone and joint disease This bacilluria may persist for a prolonged time, but spontaneous healing is always possible in this stage even without antibiotic treatment. Should the lesion persist, or enlarge and join up with other similar areas to form a caseating focus, ulceration into the calycine system occurs and this produces the first radiological evidence of the disease. Until recently this was a most important stage clinically because while there has never been a place for surgery in a tuberculous kidney without radiological evidence of an ulcerating lesion it used to be thought that once such a lesion was established it was unlikely to heal without surgery Today with the advent of antibiotic and sanatorium control the development of a demonstrable renal lesion

will we hope become of academic interest rather than a signal for surgery Many of these lesions will heal with treatment provided it is continued for long enough, and nephrectomy should never be considered without a period of observation under antibiotic therapy



FIG 71 Excretion pyelogram showing marked dilation of right lower ureter due to stenosis at the uretero-vesical junction. Practically no medium has entered the bladder

Regardless of the progress of the renal lesion if tubercle bacilli are being liberated into the urine, infection of the ureter and lower urinary tract can occur at any time Ulceration at the lower end of the ureter may cause stenosis with a closed-off pyonephrosis before any bladder or other lesion develops (Fig 71) On occasion it may be the bladder involvement which draws attention to the

disease, while in other instances, the ureter and bladder may escape completely or may heal without leaving any clinical evidence behind and an epididymitis following a focus in the vesicles may be the first and only sign of the genito-urinary infection.

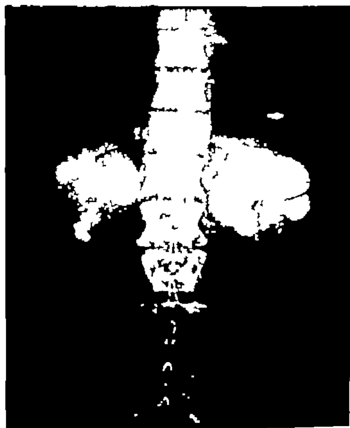


FIG 72. Calcified non-functioning left kidney discovered during a routine investigation for dyspepsia. There was a history of a transient pleural effusion twenty-one years previously Tubercle bacilli were cultured from the walls of the cavity after nephrectomy

Involvement of the vesicles or the prostate can occur very early in the disease and a recent review of Service cases (Hanley 1954) revealed that an epididymitis was the first presenting symptom of genito-urinary tuberculosis in 27 per cent of the patients.

A tuberculous cystitis will generally heal when the renal disease

becomes quiescent, but a prostatovesiculitis is unlikely to do so and this accounts for the later development of epididymitis in the absence clinically of any kidney ureteric or bladder lesion The frequent lack of any demonstrable renal lesion led many workers to support the theory of direct hæmatogenous spread to the epididymis or to the vesicles and prostate (Moore 1937) but today with some notable exceptions (Gow 1955) most urologists consider that the vesicles become infected from the kidney and are always involved before the testicles.

It has long been agreed that once a caseating focus develops true healing does not take place, though fibrosis and walling off may occur thus producing indefinite quiescence. However such a focus can always break down even if calcification is present (Fig. 72) so that treatment has been largely directed to the surgical removal of such areas of caseation

DIAGNOSIS

Detection of Tubercle Bacilli in Urine

The one and only clinical proof of a tuberculous lesion is the detection of tubercle bacilli and in the early stages when it is most useful, this is no easy matter A Ziehl Neelsen stained slide of a centrifuged deposit of urine if negative means nothing and, if positive, requires confirmation by culture or guinea pig inoculation, or by both according to some authorities. No urologist would accept a diagnosis from a stained smear alone

Pathologists are not yet agreed on the relative merits of culture versus guinea pig inoculation. Guinea pigs are expensive owing to the cost of maintenance of an animal house and technicians, etc. Two animals are generally required per examination and the result takes six weeks to obtain. Culture methods are very cheap even to perform in duplicate but they require painstaking care in the laboratory take up much centrifuge time and incubator space and although the result may on occasion be available within three weeks, the percentage of positive results may not be as high as by guinea pig inoculation.

The 24-hour specimen of urine, is now condemned as allowing too long a time for the urine to become overgrown with secondary organisms, so that an early morning urine in a sterile vessel is preferred by most laboratories and insisted upon by bacteriologists for cultural methods.

It will be seen from the previous paragraphs that the rapid and accurate detection of tubercle bacilli especially when only in small numbers, is a problem which has not kept pace with the modern treatment side of the disease. We now require much more rapid methods in order to assess the results of conservative treatment before contemplating surgery When we consider the difficulties in locating a few tubercle bacilli in an early morning bladder full of urine, one must be excused a personal scepticism about the value of a mere few ml of urine collected via a ureteric catheter

Tubercle Bacilli in Seminal Fluid

It is not sufficiently realised that the seminal fluid in a case of epididymitis may contain tubercle bacilli when the urine remains consistently negative (Obrant, 1951 Hanley 1954) Routine culture of the seminal fluid is therefore a very valuable help not only in diagnosis, but in assessing the results of treatment, since long after an apparent cure following an epididymectomy tubercle bacilli can be recovered from the seminal fluid, thus indicating that the primary genital focus in the vesiculoprostatic region is still active (Hanley 1954) A masturbation specimen is far more satisfactory for culture purposes than a few drops of mucus obtained by prostatic or so-called vesicular massage

Radiological Diagnosis

Retrograde pyelography has long held pride of place in the localisation and assessment of a tuberculous lesion, because it was always said that a radiologically demonstrable lesion would never heal and that early nephrectomy was the ideal treatment. However with the advent of antibiotic therapy and less radical surgery the accurate localisation of small calyceal lesions may be merely of academic interest in estimating the response to treatment. The important factor is the presence or otherwise of tubercle bacilli so

that repeated urine examinations are of greater importance than fine-detail X rays, particularly if these are distorted by the slight overfilling so difficult to avoid in retrograde pyelography Improved contrast media and the intelligent application of ureteric compression in excretion urography will undoubtedly reduce the need for many retrograde examinations, and most British urologists would favour this in principle. Excellent excretion pyelograms using ureteric compression in tuberculous cases have recently been shown by Ericsson and Lindblom (1950)

Aortography has been used extensively in some centres for estimating the extent of a tuberculous lesion (Weyde, 1951, 1952) but although the absence of a vascular pattern produced by a large caseating lesion can sometimes be beautifully demonstrated, the author has been disappointed with the help obtained in small lesions when trying to assess the suitability for partial nephrectomy It is probably too early to estimate the true value of this procedure in renal tuberculosis.

Genital Tuberculosis

Male

Epididymitis may be the first clinical sign of a tuberculous involvement of the urogenital tract. In the absence of any other obvious lesion an acute epididymitis may be difficult to diagnose as tuberculous until a sinus forms or the chronic stage sets in with the typical nodular hardness, but in both cases early diagnosis may be helped by the detection of tubercle bacilli in the seminal fluid. An active focus in the vesicles can remain for years without causing any apparent symptoms and the author has found the organisms persisting in the ejaculate more than ten years after an apparent cure by epididymectomy (Hanley 1954) Tuberculous vesiculitis is a cause of azoospermia the importance of which is only becoming realised with the increased interest in the male aspect of subfertility (see p 256) The risks of infecting the female partner with tubercle bacilli in the ejaculate must be extremely small as judged by the great rarity of tuberculous cervicitis or vaginitis and the relative frequency of male genital infection.

Female

Genital infection in the female is largely confined to the Fallopian tubes and endometrium the ovary cervix, or vagina being relatively immune Hæmatogenous spread is again considered responsible. Tuberculous endometritis is much more common than was previously thought as shown by its not infrequent discovery in endometrial biopsy examinations at subfertility clinics. It can be present with normal tubes so that a hysterosalpingography may not detect it, and although tubercle bacilli can be cultured from the menstrual flow a more rapid and accurate diagnosis is obtained by curettage.

The importance of a tuberculous endometritis, which may be completely symptomless, lies in the fact that, so far no patient is known to have become pregnant with such a lesion present. This gloomy picture may eventually be altered if young girls can be adequately treated at the age of fourteen to eighteen years, since the endometrium would appear to become involved during the early post primary phase of the disease (Barns, Smith and Snaith, 1953) Snaith (1955 personal communication) has now seen three certain and one probable pregnancy following adequate antibiotic treatment.

ANTIBIOTIC AND DRUG THERAPY

One of the most notable advances in recent years has resulted from the fact that the tubercle bacillus under certain conditions can now be controlled by antibiotic and chemotherapeutic means, and while surgery still forms an essential part in the treatment of genito-urinary tuberculosis, it is used only in support of the natural resources and after the degree of response to antibiotic measures has been assessed Immediate nephrectomy for example should be a thing of the past except in very advanced lesions.

It is now known that the early claims for streptomycin as a cure for tuberculosis in place of surgery were completely unfounded, and the excellent work done by Jacobs and Borthwick (1950) showed that little or only temporary relief could be given to very advanced cases These workers also drew attention to the fibrosis and contraction produced by the healing effects of streptomycin a feature not always in the patient s interests when

applied to the ureter or bladder but which explained the self limiting effects of the drug in advanced lesions where the tubercle bacilli tended to be protected from attack by the healing reaction The early conflicting reports of results from streptomycin were largely due to the varying response of different types of lesions, and for this reason the classification of Jacobs and Borthwick (1950) forms a useful basis for comparison today

Group 1 Unilateral renal tuberculosis—minor lesion without cystitis.

Group 2 Unilateral renal tuberculosis—major lesion necessitating nephrectomy cystitis

Group 3 Bilateral renal tuberculosis—nephrectomy for the more advanced lesion.

Group 4 Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease.

Group 5 (*a*) Major bilateral tuberculous lesions. (*b*) Minor bilateral tuberculous lesions.

The most serious drawback to streptomycin, apart from its toxic effects, is its ability to encourage resistant strains of tubercle bacilli, and this, combined with the fact that bacilli in fibrotic or caseous lesions were protected, thus allowing recrudescence after cessation of the drug, led to further researches. Para-amino salicylic acid, though relatively ineffective alone, was found to prevent drug resistance to streptomycin when given with the latter PAS may produce severe intestinal upset in some patients while the less toxic sodium salt is extremely unpleasant to take, but the calcium salt of nitro benzoyl PAS or calcium BPAS (Gow 1953a) is both tasteless and non-toxic in some cases

Nicotine hydrazide when first introduced was hailed as a cure for tuberculosis, but the short duration of its initial impressive effects were soon recognised and its haphazard use was condemned Joiner (1952) and his colleagues showed that in pulmonary lesions the initial improvement lasting three to six weeks was followed by a relapse with excretion of resistant forms of organisms in the sputum but if isoniazid was combined with streptomycin the initial improvement was maintained

Further light has been thrown on the subject by the work of Dick

(1953) in Glasgow who showed that isoniazid had the effect of increasing the vascularity of the lesion. He showed that the fibrous tissue which developed as a natural response to the tubercle bacilli became revascularised and concluded that the relapse which followed the initial improvement was probably due to this revascularisation which tended to liberate further bacilli into the blood-stream. Provided streptomycin is given at the same time this can be a good thing

The second M R C. report (1953) concluded that neither streptomycin, PAS or isoniazid should ever be given alone, and that a combination given to a patient with organisms resistant to one of them was the same as giving that one drug alone. Sensitivity testing would therefore appear to be essential since even new cases are sometimes infected with already resistant strains.

It is obvious that although the optimum dosages and combinations of antituberculous drugs have not as yet been worked out, the treatment of genito-urinary tuberculosis has entered upon a new phase, in that small lesions can be made to heal while the progress of larger ones can be halted even if only temporarily

General Principles of Treatment

Early diagnosis is a most important factor in the control of tuberculosis, since the response to antibiotic treatment in young people is so much better than in those late middle-aged patients who have a chronic form of the disease widely disseminated throughout the genito-urinary and, possibly pulmonary systems.

It must also be realised that healing" or cure results in fibrosis with destruction of tissue Antibiotic therapy can halt the spread of new disease throughout the kidney but the healed areas are already functionally destroyed The amount of functioning renal tissue left after cure cannot be more than was present when treatment first started, hence the importance of early diagnosis.

Unfortunately the transitory albuminuria and bacilluria of the early case is unlikely to be detected except in patients already under observation for some other form of the disease, where urines are being examined regularly as a routine measure Such cases of bacilluria, perhaps without any radiological or cystoscopic evidence

of disease, are nearly all curable with adequate sanatorium and antibiotic treatment. Even the firmly established lesion in one or more calyces will improve with such treatment, so that immediate nephrectomy should be a thing of the past

A sanatorium regime is now considered to be as important for genito-urinary tuberculosis as it is for pulmonary disease and owing to continued pressure from urologists suitable accommodation for non pulmonary cases is slowly being provided by the authorities The discipline and rest the occupational and antibiotic therapy and the mental attitude can all be so much better controlled in a sanatorium than in a general hospital, where long-stay cases inevitably become depressed by the constant changing of their more fortunate fellow patients. Quite apart from this, the prognosis of cases treated in sanatoria has been shown by Ross (1953) to be much better than those treated in general hospitals. Such a period of sanatorium treatment should last six months or longer (Lattimer 1952 Ross, 1953) during which time constant review by a urologist is necessary to decide upon the optimum time for surgery

The general public are resigned to the fact that pulmonary tuberculosis may take years to treat, but are often resentful when told that the same now applies to genito-urinary disease, even though they may have no active lung lesion It is, therefore, of great importance that the recent changes in urological opinion and in the prognosis of this disease should be explained to the patient when the diagnosis is first established He must consider his treatment in terms of years, not months, and he must understand that even after his initial term of stabilisation in hospital, with or without surgery he may require ambulatory treatment as an out patient for many years (Ross, Gow and St. Hill 1955)

A patient with a grossly diseased kidney which will obviously require a nephrectomy will benefit greatly from a preliminary course of antibiotic treatment which will often completely relieve bladder symptoms. The rapidity with which even severe tuberculous cystitis will heal if treatment is continued into the post-operative period is one of the more encouraging aspects of modern therapy and one can now hope to avert the development of a systolic bladder

It is impossible to decide what surgery will be necessary when the

patient first comes under observation, because the response to treat ment varies considerably from one individual to another A small renal lesion confined to one or two calyces may become and may remain quiescent, in that no tubercle bacilli are passed into the urine. In such a case the radiological appearances may not alter or may even look worse, but this is no indication for surgery except perhaps partial nephrectomy

It has been argued that a nephrectomy in a unilateral lesion is a once and for all procedure This is incorrect Many such men are left with a tuberculous prostatovesiculitis which can remain quiescent for years before producing an epididymitis. A man presenting with an epididymo-orchitis as his sole obvious lesion is not cured by orchidectomy because he almost certainly has a prostatovesiculitis, and thus again can flare up years later Prolonged treatment is therefore necessary regardless of surgery

The length of time for which treatment must be continued in order to achieve a cure is not yet known, but is certainly years, not months In Scandinavia, patients may be retained in hospital for a year or more even after the lesions are considered to be quiescent. In this country there is a tendency to stabilise the patients in hospital and when the urine has been tubercle-free for six months or so to continue ambulatory treatment as an out patient for as long as necessary

The patient must be kept under observation almost indefinitely but we have not yet had sufficient experience of antibiotic therapy to know the best way to treat relapses after apparent cure. For example, continuous drug treatment as an out patient can be given for two or three years on end, in spite of persistently negative urine cultures, or treatment can be given only if and when, tubercle bacilli reappear in the urine

Antibiotic Treatment

Anti tuberculous drugs may have to be given for many years, thus it is important to avoid their toxic vestibular and other effects, and also to prevent the tubercle bacilli becoming drug-resistant. For this reason Ross and Gow (1953b) gave streptomycin in a series of short repetitive courses rather than continuously while it should

never be administered alone but always in conjunction with INAH and/or some form of PAS The optimum dosage and combinations of the various drugs available have yet to be agreed upon, but most regimes are centred round streptomycin and isoniazid as the most effective agents (Gow 1953b M R.C., 1953 M R C. 1955)

The Medical Research Council trials (1955) for pulmonary tuberculosis support in principle the Ross and Gow regime for genito-urinary disease which has been used with minor modifications in many centres in this country (Gow 1953b) * However recently there has been a growing tendency to give longer continuous courses of drugs without interruption Complications or drug resistance do not appear to have increased thereby and it is possible that the modern forms of the drugs are less toxic than the earlier preparations.

Where possible antibiotic therapy should be continued for at least six months after tubercle bacilli have disappeared from the urine. This is then followed by ambulatory treatment as an out patient for a further six months, but the patient should be kept under observation indefinitely in the present stage of our knowledge.

Surgery

Surgery may become necessary at any time during the course of treatment or observation but each patient must be treated as a separate problem.

An early unilateral lesion associated with mild bladder involvement should no longer be subjected to immediate nephrectomy since this is the type of case in which one could hope for a cure, or at least control, by conservative measures alone. However certain progressive or sudden pyelographic changes, such as signs of contraction and obstruction at a calycine neck, at the pelvi-ureteric junction, and at the ureterovesical junction are of great importance

Such mechanical obstructions call for early surgery even when treatment has rendered the urine tubercle free because the kidney

* Streptomycin, 2 G daily 1 dose; Isoniazid, 250 mgm daily 1 dose — 2 weeks
Thiosemi carbazone, 100–120 mgm. t.d.s. daily; B P.A S 7 G t.d.s. daily — 2 weeks
Note.—The use of thiosemi carbazone has now been discontinued.

can be destroyed by back pressure even while its tuberculous lesion is healing.

While contraction of the pelvi-ureteric junction (Fig. 73) generally calls for nephrectomy obstruction near the ureterovesical junction should be treated by early excision of the stricture and reimplantation of the ureter into the bladder It is important, however to decide whether radiological dilatation at the lower end of the ureter



FIG. 73 Progressive obstruction at the right pelvi-ureteric junction. Uninfected left double kidney

really is due to obstruction (Fig. 74) If it is due to ureteric reflux from a contracting bladder reimplantation will not help the situation and some form of ileocystoplasty should be considered. When contraction occurs at a calyceal neck a pyocalyx results and this may be an indication for a partial nephrectomy

Partial Nephrectomy

In carefully selected cases this operation has a most important place in the treatment of renal tuberculosis, since conservative

surgery in a potentially bilateral disease is all important The danger of leaving areas of unsuspected infection behind may not be so

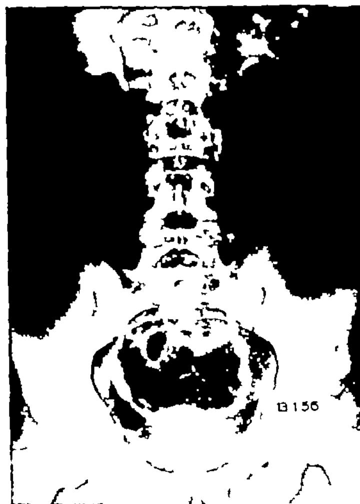


FIG. 74 Bilateral renal tuberculosis with systolic bladder Multiple stricture formation at lower end of left ureter Micturating cystography showed that the dilation at the lower end of the right ureter was due to reflux rather than stricture formation.

serious as one might think, provided adequate sanatorium treatment is available because there is good evidence to show that lesions too small to give radiological changes will heal with streptomycin etc.

In bilateral renal cases, the need for conservatism is even more important, and it is now possible to remove one grossly diseased kidney and a portion of the remaining one or even to perform a partial nephrectomy on both kidneys (Semb 1949 1953 Hanley 1950) However many urologists in this country are so impressed with the results of antibiotic therapy alone that distorted calyces which would have been resected a year or so ago are now being left in situ provided they are " open, and the urine is tubercle free (Hanley 1957b)

It is too early to estimate the long term results of partial nephrectomy in renal tuberculosis, but there are several series of cases now under observation, and this information will undoubtedly be available in due course (Semb 1949 1953 1956 Hanley 1950 1957a Lattimer 1952, 1956 Jacobs 1953 Ross, 1953 Cibert, 1953)

Nephrectomy

For whatever disease this is an admission of failure

However when confronted with failure urologists agree that if the ureter is seen to be involved at the time of nephrectomy a complete nephro-ureterectomy should be performed It should be noted that ureteric obstruction usually starts at the lower end, and that the dilatation progresses from below upwards. An early stricture at the lower end of the ureter may not have produced any demonstrable effects in the upper portion by the time the nephrectomy is performed. If however a long ureteric stump is left *in situ* this stricture will become tighter and will often produce trouble later on. Persistent holdup of the opaque medium in the lower ureter during excretion urography is often more reliable evidence of pathology in this region than direct observation of the condition of the upper ureter at operation.

Ureteric Obstruction

In many cases the renal lesion responds well to drug therapy but progressive stricture formation at the lower end of the ureter may still destroy the kidney There are encouraging reports of the resection of this portion of the ureter with reimplantation into the

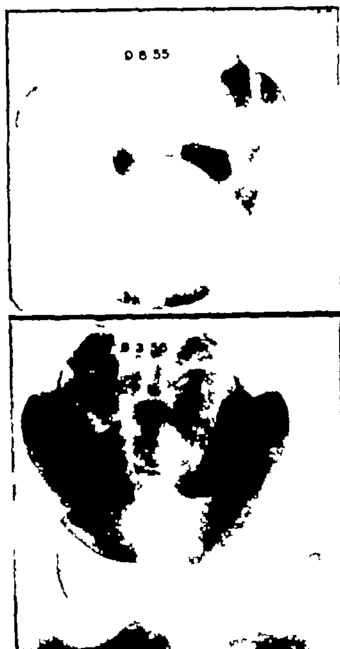


Fig 75 Progressive contraction of the bladder in spite of sanatorium treatment and the removal of the grossly diseased right kidney Uninfected left kidney

bladder (Puigvert, 1955) and more work will doubtless be published on this subject (Fig. 74)

Contracted Bladder

One of the most disabling complications which can follow renal tuberculosis is the contracted or systolic bladder Even after a



FIG 76. Extensive calcification in long standing contracted tuberculous bladder

nephrectomy has removed the primary source of tuberculous infection and even though the remaining kidney be free from infection, a severely ulcerated bladder may continue to contract (Fig. 75) Eventually its capacity is so reduced that frequency is increased to the point of incontinence, while severe back pressure effects on the remaining kidney finally prove fatal.

Modern antibiotic therapy generally provides rapid relief of

symptoms in early cases of tuberculous cystitis, and it is to be hoped that, if ulceration can be controlled before it has extended through the mucosa to the muscular layers, the subsequent development of a systolic bladder may be avoided.

Unfortunately the antibiotic agents are not of great help once the bladder has become contracted due to fibrosis as opposed to spasm (Fig. 75) or where calcification has occurred (Fig. 76) but by controlling the active tuberculous ulceration these drugs have made possible certain types of surgery undreamed of only a few years ago In place of intestinal or cutaneous ureterostomy plastic operations on the bladder itself have been performed both to increase its storage capacity and to overcome ureteric obstruction, and the preliminary reports in many cases are encouraging. These include ileocystoplasty which is discussed on page 200

Future Developments

The search for new or improved antibiotic drugs continues Oxytetracycline (terramycin) has been found to delay or prevent the onset of streptomycin resistance (Rothstein and Johnson, 1952) and of isoniazid resistance in pulmonary tuberculosis (Stewart, Turnbull and Croften 1954)

Barry (1955) has produced some interesting antituberculosis agents by condensing isoniazid or p-amino-benzol-thiosemicarbazone with polysaccharides which have been oxidised by periodate, and developments along this line of research will certainly continue.

It is hoped that the next few years will produce further great advances in the conservative treatment of genito-urinary tuberculosis.

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CHAPTER 13

SURGERY OF THE ADRENAL GLANDS

THE surgery of the adrenal gland is of especial interest to the urologist, since many of the investigations employed in a general urological practice such as pyelography perirenal insufflation and renal arteriography may be invaluable in the diagnosis of adrenal pathology Apart from this, the surgical exposure of the adrenal gland presents no new problem to the urologist, who is used to overcoming greater difficulties in this area than those generally associated with adrenal surgery (Figs. 77 and 78)

Until quite recently the complete removal of both adrenal glands resulted in death. The removal of one adrenal was a hazardous procedure unless special precautions were taken to ensure that there was another gland on the other side while attempts to reduce the overall functioning tissue by bilateral partial resections were always hit or miss."

However the introduction of cortisone by providing adequate cortical replacement, gave a great impetus to adrenal surgery and, although all of today s indications for total adrenalectomy may not stand the test of time, the researches that have been made possible may well lead to great advances in the study of cancer hypertension and endocrine disturbances in the near future.

Adrenogenital Syndrome

This is chiefly encountered in childhood in the form of the female pseudo-hermaphrodite and is due to adrenal cortical hyperplasia More rarely it may be due to a tumour of the cortex, and the differential *diagnosis may be extremely difficult In both cases the total* urinary 17 ketosteroids are increased If however cortisone is administered, the urinary 17 ketosteroids are reduced to normal in cases of simple cortical hyperplasia but are not affected in the presence of cortical tumours (Hodges, 1953) This is a most

important diagnostic point, since the hyperplasia can be treated very successfully by cortisone therapy alone (Williams, 1954), while adrenalectomy is the only hope for the tumour cases

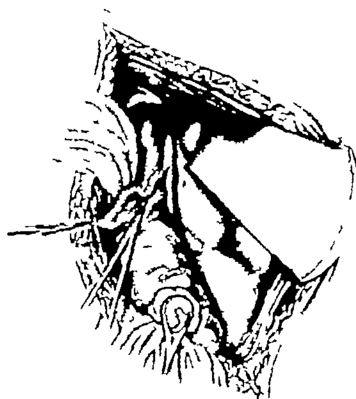


FIG. 77 Exposure of right adrenal gland through the bed of the twelfth rib The kidney is being pressed downwards thus exposing the vena cava and the adrenal gland with its blood supply which is extremely variable. On occasion the veins are very short, making separation of the gland from the vena cava difficult.

Cushing's Syndrome

Whether this condition is due to bilateral hypertrophy of the adrenals or to cortical tumours, surgery is the treatment of choice.

In hypertrophy cases the whole of one gland and most of the other is removed, the operative procedure being rendered relatively uneventful provided that adequate pre and post-operative cortisone

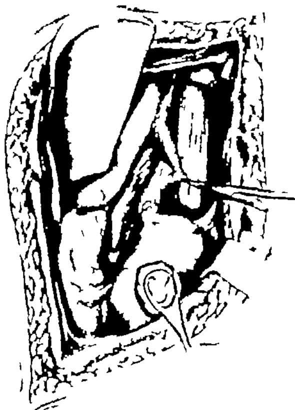


FIG 78 Left adrenal gland. *The blood supply is extremely variable.* Vessels may come from the region of the crus of the diaphragm, the renal vessels or the aorta. The case illustrated had a leash of separate arteries arising directly from the aorta.

replacement therapy is used In the tumour cases the opposite gland is almost invariably atrophic, but here again the introduction of cortisone has rendered the post-operative course much smoother and safer

Phæochromocytoma

These tumours, though generally arising from the adrenal medulla, may also occur in any sympathetic ganglion tissue so that they are not infrequently multiple (16 per cent are multiple according to Cahill (1953)) and may be found anywhere along the aorta or its main branches. In fact Zimmerman (1953) and his colleagues described a case presenting as a pedunculated tumour in the bladder causing hæmaturia.

Although the classical syndrome of these tumours is one of paroxysmal hypertension they may produce a sustained rise in pressure and the clinical picture is then identical with essential hypertension. Pharmacological tests are very valuable in diagnosing these tumours, but false results may occur if various other drugs such as narcotics, sedatives and the new hypotensive agents are given at the same time Kyale (1954) found that histamine was the most reliable test drug to use in the paroxysmal cases, while phentolamine and piperoxan were the best in sustained hypertension. He also points out that multiple tumours and malignant tumours are commoner in the sustained than in the paroxysmal types of hypertension, while at operation, if there is not a marked fall of pressure when the mass is removed, one should suspect the presence of further tumour tissue. Most writers on this subject recommend an anterior abdominal approach so that an extensive search can be made for accessory tumour masses.

The pre-operative radiological demonstration of a large tumour either by aortography or perirenal insufflation is very helpful, but even the existence of one large mass does not exclude the presence of other smaller ones, while the radiological findings will always be negative with small tumours.

Total Adrenalectomy for Malignant Hypertension

The availability of cortisone has led to a renewed interest in the problem of treating malignant hypertension by adrenalectomy In the past varying results have been claimed for this type of surgery which generally took the form of a total removal on one side and a subtotal resection on the other If too much glandular tissue was

left *in situ* the effect on the blood pressure was negligible, while if too much was removed, death ensued Adequate replacement therapy has altered all this and bilateral total adrenalectomy is now a relatively safe surgical procedure In favourable cases the hyper tension is reduced, while in a majority of patients symptomatic relief of the cardiac failure the papilloedema and the headaches is so marked as to make the operation worth while even if the pressure is unaltered

Very severe arteriosclerosis may prevent a fall in the diastolic pressure, and is considered by some to be a contra-indication to adrenalectomy (Crooke 1954) However it is not always possible to decide before operation whether the arteriosclerosis is too advanced or not, and much more experience is necessary in this field The one definite contra indication to surgery is renal failure Once failure is established (urea clearance of under 50 per cent (Harrison, 1952)) it is progressive and the patient dies in uraemia, in spite of a reduction in hypertension cardiac failure and any other symptoms.

Several encouraging reports have appeared in the literature recently especially one from Hartwell Harrison and his colleagues (1952) which the author can support from personal experience (Hanley 1954) So far only cases of established and often advanced malignant hypertension have been operated upon. Severe cardiac failure and extensive eye changes are no bar to surgery being in fact dramatically improved by the operation but renal failure is an absolute contra indication and in the author s view no further progress will occur in this particular field unless surgery can be performed at a much earlier stage, preferably before or when the first rise in blood urea is detected

There are many unexplained features of this problem quite apart from the fact that we do not know the mechanism whereby adrenal ectomy produces such a marked clinical improvement in these patients, and it is becoming increasingly obvious that the hyper tension *per se* is not the important factor In the author s experience there is no guarantee that the blood pressure will fall after operation but the clinical improvement can be dramatic and prolonged (Barnes, 1956)

Adrenalectomy in Diabetes

It has been known for some time that adrenal cortical function is disturbed in diabetes (Wortham and Headstream, 1953) and that this disturbance is probably due to the degenerative vascular changes, which are prone to occur especially in the younger patients

The earliest signs of diabetic vascular changes are detectable in the retinal vessels, and are followed by a generalised arteriosclerosis which precedes hypertension, progressive blindness, and renal failure.

Bilateral adrenalectomy has given encouraging results in such cases (Headstream and Wortham, 1955) and the author can vouch for the dramatic improvement in vision which may result. Here again however surgery must be carried out before severe renal damage has occurred, and there must be much closer liaison between physician and surgeon if further progress is to be made.

Adrenalectomy for Cancer

The beneficial effects of castration in cases of carcinoma of the breast and prostate have been recognised for several years. In the same way the administration of the male sex hormone to female breast cancers, and œstrogens to male prostatic cancers, has demonstrated the very close link between these types of growths and the endocrine system, with the result that they are now considered to be hormone dependent cancers. It was also known that castration stimulates the adrenal cortex to replace the particular hormone originally produced by the gonads, male or female so that the next logical procedure was to try and remove all the adrenal cortical tissue as well as the gonads. Until quite recently this was impossible in the human patient, since before the advent of cortisone life could not be sustained without the presence of some adrenal tissue

To Huggins (1945) must go the credit for pursuing these theories relentlessly during the years before adequate replacement therapy was available, and for eventually presenting a series of quite hopelessly inoperable breast and prostatic carcinomas whose lives had been rendered infinitely more comfortable following total adrenalectomy and cortisone replacement therapy (Huggins and Bergenstal, 1951 1952)

Since then the procedure has been adopted in centres all over the world where cortisone is available

H T Cox (1947) was the first British surgeon to perform a total bilateral adrenalectomy for carcinoma of the prostate but since then several series have been reported (Cade, 1954 Fergusson 1954 Hanley 1954b Pyrah 1954) and it is now possible to form some idea of the value of the procedure

Prostatic cancer can be very adequately controlled for many years by œstrogen therapy and orchidectomy and no urologist would recommend adrenalectomy as a routine procedure However where there are extensive bone and visceral metastases or when the disease looses its response to œstrogens, then adrenalectomy may afford the patient marked relief of pain and some increased expectancy of life. In general, however, the results in prostatic cancer have been disappointing.

In contrast to prostatic cancer the results in breast cases are more encouraging, and the author has one patient alive, well and active nearly four years after adrenalectomy at which time she had multiple skin and bone metastases, bilateral pleural effusions and an ulcerating breast growth which has since healed

So far only growths which are inoperable or which have recurred after surgery or radiotherapy and which may have extensive metastases, have been treated by adrenalectomy but in spite of this stringent selection the results have been dramatic in many cases, but here again the ultimate end is only delayed.

It may be that in future we should operate upon these cases earlier or that we should attack the pituitary gland instead of or as well as, the adrenal gland, but at least this work has centred attention on the hormone dependent tumours from another aspect.

Substitution Therapy

The removal of both adrenal glands causes death unless adequate replacement therapy is carried out with cortisone Huggins and Bergenstal (1951) described their routine system of pre and post operative therapy which consisted of

Day before operation Cortisone, 50 mgm 6-hourly DOCA 3 mgm.

Day of operation	Cortisone, 150 mgm. 1 hour before operation.
	Cortisone, 50 mgm. 4-hourly after operation.
	DOCA 5 mgm.
Operation day + 1	Cortisone, 50 mgm. 6-hourly
	DOCA, 5 mgm
" + 2	Cortisone, 50 mgm. 12 hourly
+ 3	Cortisone, 50 mgm 12 hourly
" + 4	Cortisone, 50 mgm. 12 hourly
, + 5	Cortisone 50 mgm. 12 hourly

Although many surgeons have made minor modifications, the general principle remains unaltered, although DOCA would not appear to be necessary provided salt loss is corrected, while many surgeons prefer to give cortisone by mouth for at least forty-eight hours prior to operation Absorption from the gut would appear to be more effective than from the muscles.

It is generally possible to maintain patients on a cortisone dosage of 25 mgm. twice daily after the first week. Sodium chloride (3 G) should be given in tablets or capsules to combat the danger of excessive salt loss. This subject is dealt with more fully in the chapter on carcinoma of the prostate

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CHAPTER 14

SUBFERTILITY

It can be admitted at the outset that the many recent advances in our knowledge of human subfertility have been largely concerned with the innumerable causes rather than with any dramatic improvements in treatment.

One major advance, however is the realisation that the male is probably at fault in a subfertile marriage quite as often as the female partner so that the responsibility of investigating and treating this problem rests with the urologist just as much as with the gynæcologist

This is quite a new conception, since in the past a case of oligozoospermia was referred to the endocrinologist, while azoospermia was considered hopeless, but today the urologist can often help such patients at least as much as the endocrinologist, so that a close liaison between the three specialities and a full investigation of both partners is essential in any subfertile union

Before a normal conception can occur normal spermatozoa must come into contact with a normal ovum whilst it is in the Fallopian tube or uterine cavity It is believed that though the ovum only lives for about twenty-four hours, the spermatozoa can survive for several days in the female tract. Intercourse must therefore take place at or just before ovulation if fertilisation is to occur Explanation of these simple facts will frequently result in an immediate pregnancy in women who have failed to conceive though both partners are normally fertile

Ovulation

Most women ovulate on the 11th–14th day of the menstrual cycle The body temperature usually rises several points of a degree in the second half of the cycle and the actual time of ovulation is frequently marked by a sudden drop followed by a sharp rise as shown in Fig. 79 The keeping of such a chart gives much useful information

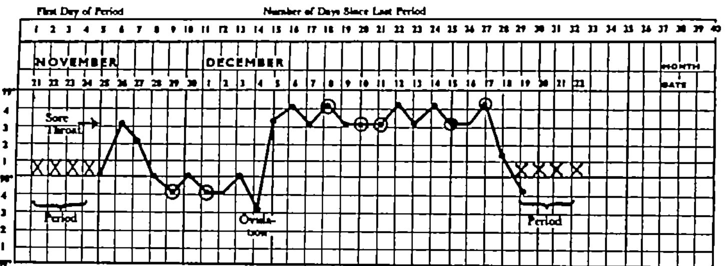


FIG 79 Basal temperature chart. Readings taken per rectum or per vaginam at the same time every morning, before rising, and before eating or drinking. (Reproduced by permission of Ortho Pharmaceuticals, Ltd.)

in the study of these cases, though the estimation of the actual time of ovulation is not always reliable Many women do not ovulate with each cycle, while the actual day of ovulation may vary and a more accurate estimation of this date would be invaluable in treating certain types of disorders

Farris (1951 1946) has introduced a rat test which he claims is accurate to within a few hours The patients urine is injected daily into a special Wistar rat which is killed shortly afterwards. If ovulation has occurred the injected urine produces a hyperaemia of the rat ovaries readily detectable macroscopically Although this test is of great academic interest, it is always likely to be too expensive to employ as a routine measure in this country

Various other changes occur at ovulation such as the alteration in the consistency of the cervical mucus which, though normally thick and opaque with a high cellular content, becomes thin and clear with very few cells present. In most women the mucus is only receptive to the sperms when in this condition (Jackson *et al.*, 1948)

Alterations in cervical mucus, including the existence of a definite cervical hostility to sperms, are considered very important by several workers (Barton and Wiesner 1946 Shotton, 1951)

Post-coital Test

Although sperms are rapidly killed by the normal acid vaginal secretions, examination of the cervical plug of mucus 12–36 hours after intercourse at ovulation time will show millions of actively mobile sperms If this test (Huhner 1913) is positive the male partner is unlikely to be at fault, but if the sperms are scanty sluggish or absent, further investigation is necessary A post-coital test is frequently the simplest and quickest way of discovering difficulties in the sexual act which no amount of questioning can elicit.

Semen Examination

Macleod (1950) examined 1 000 men whose wives had conceived, and were therefore known to be fertile and found that under such circumstances 20 million sperms per ml was the lowest limit of

normal. It is obvious that there is no sharp dividing line and that a high degree of fertility in the woman can compensate for a low sperm count and vice versa Several instances are recorded where conception has occurred in spite of extreme oligozoospermia under the million per ml (Moore-White and Barton 1951) and this in association with the fact that the count can vary enormously over a short space of time (Kennedy Richards and Bishop 1951 Davidson, 1952) should make one very guarded in giving a quite hopeless prognosis to a man who has any live sperms, and also in assessing the value of a particular form of therapy

Much important work has been done recently on the morphology of spermatozoa, and upon the methods of counting and estimating motility (Hotchkiss, 1945 Harvey and Jackson 1945 Davidson 1949 Barton and Wiesner 1946) Unfortunately many reports upon a sperm count are practically valueless and, to quote Davidson (1952) *a semen report which states that spermatozoa are present and motile is as completely meaningless as a blood count which informs us that red and white blood corpuscles are present.*

Davidson considers that the minimal data which a report should provide are

(*a*) How the specimen was collected—a condom specimen is useless.

(*b*) The age of the specimen. If over two hours the motility figures mean nothing.

(*c*) The volume density of sperms per ml Percentage motility and incidence of morphological abnormalities.

The volume is important because if it is below 1 5 ml too much may be lost in the vagina if the ejaculate was not directed at the cervix. Also the buffering action of the seminal vesicular fluid may not be able to protect the sperms against the normally acid vaginal secretions. In an excellent account of his experiences with over 7,000 analyses, Davidson (1951) found that the lower limit of normal sperm density in his series was 40 million per ml., while the average motility figures ranged from 40 to 60 per cent anything over 70 per cent being very rare 35 to 40 per cent of abnormal forms were found in the semen of fertile men while less than 10 per cent was uncommon a higher incidence than 50 per cent probably indicates

other less easily detectable flaws in the whole sperm population, and he considers there is some evidence that fertilisation by such semen may lead to spontaneous abortion This view is held by many but as yet there is no statistical proof of the assumption.

In quite recent years the biochemistry of the seminal fluid has been studied by various workers, and reviewed by Mann (1949) The spermatozoa is dependent for its survival on nutrient substances in the seminal plasma and perhaps from the female tract. Fructose, formed chiefly by the seminal vesicles, is a vital constituent of the seminal plasma and undergoes elaborate changes under the influence of the enzymes in the sperm cells thus providing a source of energy while citric acid and acid phosphatase are added to the seminal fluid by the prostate Castration or nutritional deficiency completely abolish the secretion of fructose citric acid and phosphatase into the seminal plasma (Lutwok Mann and Mann, 1950) but how important this is clinically we do not know An interesting physiological fact is that the sperms do not normally come into contact with the seminal fluid until ejaculation takes place, so that these biochemical factors cannot influence the maturation or storage of the sperms previous to this occurrence.

Attention has recently been paid to the release of hyluronidase by sperm cells but it is uncertain as yet whether this phenomenon is concerned with the penetration of the ovum or not (Kurnock, 1950)

Testicular Biopsy

A testicular biopsy can be carried out under local anaesthesia if desired, but its value in the treatment, as opposed to the research, of male sterility is being doubted by many workers (O Connor 1954 personal communication) In cases of oligozoospermia repeated semen examination by an experienced seminologist will be much more reliable than a biopsy while in cases of azoospermia a clinically well developed testicle will nearly always show evidence of some spermatogenesis on biopsy The converse is unfortunately not true and I have encountered several men with counts ranging up to 5 million per ml where the biopsy sections presented a picture in keeping with almost complete azoospermia.

Mumps

A mumps orchitis at puberty or later will produce testicular atrophy for which there is no cure The atrophy is thought to be due to intratesticular tension for which incision into the tunica albuginia was recommended by Wesselhœft and Vose (1942) but Charny and Meranze (1948) from their pathological investigations did not consider that pressure was the cause of the atrophy More research is required into this problem if only to discover why every so often a mumps orchitis is not followed by atrophy From the treatment point of view incision or multiple puncture of the tunica as recommended by Kenneth Walker (1948) should be seriously considered since immediate clinical relief is afforded and at least no harm is done.

An orchitis followed by atrophy and clinically similar to mumps may develop without any parotid swelling. Of greater importance is the fact that many cases of inexplicable orchitis occurring in infants, unassociated with parotid swelling, may be due to mumps. The author has observed three such cases which were all followed by testicular atrophy while Connolly (1953) has reported three well documented examples supported by serological tests. Even so in a review of nearly 500 subfertile men (Hanley 1955) only one case of complete sterility resulted from bilateral mumps orchitis There were twelve unilateral atrophic testicles due to mumps, but the cause of the subfertility lay in the other testicle in each case.

The commonest cause of a poorly developed testicle throughout the series was delayed or incomplete descent.

Undescended Testis

It has long been accepted that a man with bilateral undescended testes will be sterile and that such testes should be brought down before puberty if normal development is to occur It is very doubtful whether a truly undescended testicle will ever come down spontaneously at puberty In fact Scorer (1955) has shown that the incidence of undescended testicles in 2 000 full term infants was 4 per cent and that the majority of these 4 per cent descended by the third month. After three months descent was slow and incomplete. By the end of one year only 0 7 per cent were still retained

and this figure is so close to the incidence of the condition in adults (given by many workers) that Scorer concludes that complete descent does not occur after the first year and probably only rarely after the third month. My own observations show that even if a "retractile" testicle does eventually stay down, it is generally poorly developed.

Delayed surgery is acknowledged as valueless if the testicles are not already well developed, and even then the prognosis is poor. It is probable, therefore, that many orchiopexy operations are performed too late and that the best time is well before (2–3 years old) not just before puberty. A factor not generally realised is that even an apparently successful result from orchiopexy may be merely cosmetic as far as spermatogenesis is concerned.

However Davidson (1952) has seen several patients whose fertility was at least adequate following orchiopexy operations and every effort should be made to bring testes into their normal position well before puberty.

Complete Azoospermia

One could assume from the French and American literature that gonorrhœa is the chief offender in male sterility but this is certainly not so in Britain. A recent survey of 148 cases of azoospermia (Hanley 1955) showed that the commonest cause was some congenital defect in the conducting system. Gonorrhœa was responsible in only 9 cases. Tuberculous prostatovesiculitis and bilateral mumps orchitis accounted for 14 and 1 case respectively while trauma accounted for 9 more. Total azoospermia with clinically developed testes and no history of an epididymo-orchitis is probably due to some congenital obstruction or error of sperm conduction. If the ejaculate volume is normal this obstruction is unlikely to be in the region of the ejaculatory ducts but rather at the testicular end of the vas.

Several instances of complete absence of the vas have been recorded recently by Young (1951) Merren and Kelly (1952) Hanley (1955) and others, while failure of union of the vas and epididymis, or of the epididymis and body of the testicle, are all described and are probably much commoner than we realise (Fig. 80).

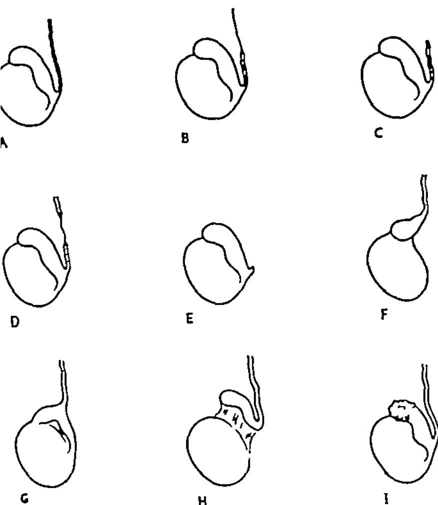


FIG. 80. The various congenital anomalies of the vasa deferentia and epididymes discovered in a large series of azoospermic males. (Hanley H. G., from *Ann. Roy Coll. Surg Eng.*, 1955 17 159)

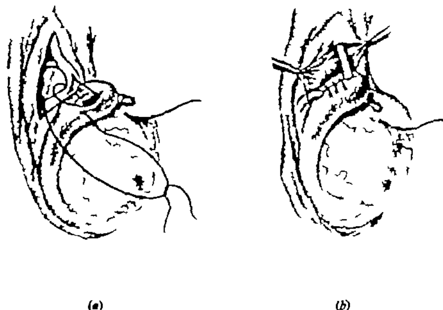
Treatment of Azoospermia

Gonorrhœal obstruction in the tail of the epididymis can be over come by epididymo-vasostomy provided the vas is patent and a success rate of 70 per cent or more can be expected (Fig 81)

Traumatic damage to the vas deferens can be repaired with success provided the ends can be approximated without tension, and this

fact should be more widely known (O Connor, 1948 Handley 1950 Humphreys, 1953 Hanley 1955)

Unfortunately the majority of cases are due to some congenital lesion, and even if an anastomosis can be established between the



(a) (b)

FIG. 81 Author's modified epididymo-vasostomy operation. An eliptical opening is cut in the vas and its patency tested by injecting saline. A monofilament nylon splint is used largely to hold the stoma in position whilst the vas is buried in the epididymis. No sutures are inserted in the region of the stoma. The splint is withdrawn in about five days. (Hanley 1955).

(a) Showing eliptical opening in vas with nylon splint *in situ*. First burying suture about to be tied.

(b) Completed procedure showing nylon splint emerging from body of testis.

vas and the head of the epididymis, there may be a fault further back in the vasa efferentia, or the mechanism of sperm propulsion may be at fault.

This problem requires much more research, probably along the lines of the formation of a skin fistula or pouch (O'Connor 1953)

or an artificial spermatocele (Young, 1951 or Hanley 1955) from which artificial insemination can be carried out

Oligozoospermia

Much has been written on the causes and treatment of oligozoospermia but we still do not know why so many millions of spermatozoa are necessary to enable one of them to effect fertilisation Opinions vary about the numbers which constitute the lower limit of fertility but a count of under 20 million per ml can be regarded as subfertile (Macleod 1950) However fertilisation can and has occurred with counts even under a million (Moore-White and Barton, 1951 Hanley 1955)

Testicular Temperature Control

Spermatogenesis can be affected by many factors, among which are small variations in testicular temperature. The classical experiments of Moore and Oslund (1924) and Phillips and McKenzie (1934) showed that characteristic seminal degeneration occurred in rams whose scrotums were insulated from the external temperature Gunn and his colleagues (1942) confirmed this work and found that the effects were not apparent in the semen unless the scrotum had been insulated for at least 5 days. However quite recently in Cambridge, Glover (1955) has shown that the elevation of testicular temperature by 5° C. for only 24 hours resulted in the sudden appearance of tailess spermatozoa 19–24 days after the experiment.

Davidson (1954a) has shown that in man the wearing of Y front underpants which hold the testicles in close contact with the body surface has a depressant effect on sperm maturation while repeated cold sponging of the scrotum has the opposite effect.

One of the main functions of the scrotum would appear to be the regulation of testicular temperature The cremasteric and dartos muscles are capable of very marked and rapid contraction or relaxation, by which means they can alter the position of the testicles, thereby maintaining their temperature below that of the body generally Anything which interferes with the heat loss from the scrotum results in elongation of the muscle fibres A *varicocele* acts in this way and accounts for the long flabby scrotum and low

testicles found in this condition. In the same way a *hydrocele* will also prevent loss of heat from the scrotum. An important feature about hydroceles is that small ones are extremely difficult to detect since they may not transilluminate but even 5–6 ml. of fluid are

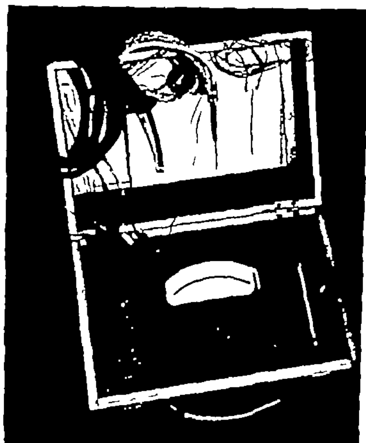


FIG 82. Differential temperature measuring apparatus (Cambridge Instrument Company). On the lid of the instrument from left to right can be seen the rectal thermo-couple, the needle thermo-couple and an ordinary skin thermo-couple.

enough to alter the normal temperature differential by 2° C or more

The marked difference between the normal intrascrotal temperature and the general body temperature in the human male can be demonstrated by means of a needle thermocouple and a calibrated galvanometer. Such an apparatus is shown in Fig. 82. The resting

body temperature is recorded by a rectal thermacouple. Skin temperatures can also be recorded from various sites, while the intrascrotal temperature is recorded by a needle thermocouple (Fig. 83) Whereas there may be a difference of up to 3 C. between the intrascrotal and rectal temperature in the normal male a differ ence of as little as 0 2 C. has been recorded in a large varicocele (Hanley 1956)

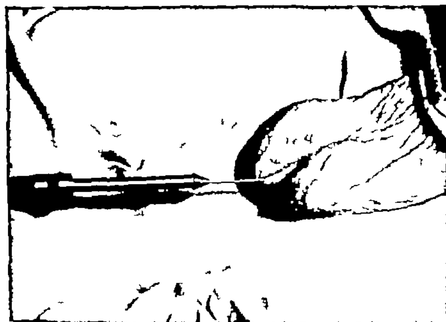


FIG. 83 Needle thermo-couple inserted into scrotal sac. A separate needle can be used to record the temperature from each scrotal compartment, but in practice the temperature difference between the two sides is too slight to be of importance.

Varicoceles and Hydroceles

Although minor degrees of these two surgical conditions are relatively common in normal young men they usually have no demonstrable effect on their fertility This can easily be understood when we remember that the sperm count in the normal fertile male ranges from as low as 20 million up to 200 million and more per ml. A varicocele will probably be a serious factor in the first instance

but could lower the count in the second instance by 50 per cent and still not affect fertility

There is now convincing experimental and clinical evidence that a varicocele, and/or hydrocele can cause severe depression of spermatogenesis in some men (Tulloch, 1952 Davidson, 1954 Russell 1954 Hanley 1955 1956) and that this can be improved or cured by adequate surgical treatment of the varicocele or hydrocele (Davidson 1954b Hanley 1956)

The sperm counts in men with subfertility due to a failure of temperature regulation are fairly typical There is normally though not always, an oligozoospermia well below 20 million per ml while Davidson (1954b) describes an increased semen volume, impaired morphology and motility and an excess of desquamated precursors of spermatozoa. If this picture is found in a physically normal man with reasonably developed testicles, whose only other clinical finding is a varicocele or hydrocele one can state that he will certainly be no worse following excision of his varicocele, while he may well be rendered fertile In actual fact where these standards have been adhered to operation has improved the counts in 70–80 per cent of the cases and has resulted in many pregnancies in previously sterile couples (Hanley and Davidson, 1956).

Surgical Treatment of Varicocele

Much valuable work on the blood supply of the testicle, etc., has recently been published by Harrison (1949) and Macmillan (1953 1954) who pointed out that in the inguinal portion of the cord the arteries are still large channels, easily seen and easily avoidable so that resection of the pampiniform plexus should be theoretically safer if performed through an inguinal than a scrotal incision. Indeed, the classical operation for varicoceles consists of resecting a third, or other fraction of the thickness of the pampiniform plexus *via an inguinal incision* However I long ago abandoned this approach owing to the occasional development of a hydrocele following ligation of the vessels at this level.

In the small or doubtful varieties a local excision of the separate varicosities one by one through a scrotal incision has proved effective. It should be noted that the offending veins are generally accessory

to the vessels contained within the fascial sheath of the pampiniform plexus. Indiscriminate ligation of a portion of the pampiniform column itself is to be condemned

The pampiniform plexus drains into three main channels, namely the cremasteric, deferential and spermatic, the most important being the last two The spermatic veins are generally responsible for the varicosities so that these are normally the only ones which require ligation In order to achieve this it is necessary to expose the vessels above the internal inguinal ring. At this site the spermatic veins have separated away from the deferential artery and veins and the vas itself and can be divided in perfect safety

The spermatic artery can also be sacrificed with impunity at this level, but in actual practice it is generally a simple matter to preserve it when the veins are being tied

In cases where the whole cord is thickened due to increased infiltration or in the large pendulous varicoceles without hydrocele formation such a high ligation is the operation of choice.

High Ligation of Varicocele

A small 4 cm. incision about 3 cm above the internal ring is deepened through the fascia and the underlying muscle layers are separated down to the extraperitoneal fatty tissues If this opening is made 2 cm above the internal ring the spermatic vessels are seen running immediately under the abdominal muscles to enter the ring, while the vas and its own vascular bundle can be palpated as they come up from the depths to join the cord and can be easily avoided (Palomo 1949)

The patient can be allowed out of bed immediately after operation and, apart from some scrotal œdema in the first few days, the post operative discomfort is negligible

Hormone Treatment

Apart from the work on temperature control, few recent advances have occurred in the treatment of oligozoospermia, though many of the older drugs and hormones have been discredited Vitamin E appears to be valueless in the male while testosterone can produce complete sterility and should never be prescribed without the

guidance of an endocrinologist or for some specific indication Swyer (1953) has recently claimed that subcutaneous implants of testosterone (300 mgm.) caused a significant increase in the motility and sperm density in twenty-eight out of a series of fifty-six males whose counts were just around the lowest limit of fertility (15–20 million per ml.) Cases of extreme oligozoospermia or asthenospermia did not respond

The marked depression of spermatogenesis produced by large doses of testosterone is said to be followed by recovery if the administration is stopped in time In some instances the count has risen above the previous level and this phenomenon has been described as spermatogenic rebound Heckel (1951 1952) treated forty four patients with intramuscular testosterone propionate, until the counts approached azoospermic levels. Eighteen of the men who were fully controlled and followed up subsequently showed a return to or above the normal levels This work has not been fully confirmed in this country where it is considered that caution should still be used

Oral Contraception

Although contraception may seem out of place at the end of a chapter on subfertility its importance for the world as a whole may be of much greater import

The value of a reliable contraceptive for oral use in the areas of gross under nourishment and over population, might be very great indeed Much animal work has already been done, and it is thought that the presence of hyaluronidase is necessary to enable the sperm to penetrate the gel around the ovum (McClean and Rowlands, 1942 Rowlands 1944 Swyer 1947) In 1952 Martin and Beiler found that phosphorylated hesperidin inhibited the enzyme action of semen hyaluronidase and effected an 80 per cent reduction in the conception rate of their rats The action was on the female rat and did not interfere with the œstrus cycle Sieve (1952) in an apparently well controlled experiment administered phosphorylated hesperidin to 300 known fertile couples and was able to prevent conception until the drug was discontinued after which a further pregnancy ensued in 41 per cent The only failures were in two couples who did not

take the tablets. The drug takes ten days to become effective but fertility returns within forty-eight hours of cessation and it is non toxic even in amounts twenty times the required dose Should these experiments be confirmed even with a much lower success rate, Sieve s work may turn out to be of importance

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PRINTED IN GREAT BRITAIN BY THE WHITEFRIARS PRESS LTD
LONDON AND TONBRIDGE